SS-31 (Elamipretide)

A Clinical Learning Guide for Medical Providers

Mitochondria-Targeted Cardiolipin Tetrapeptide • D-Arg-Dmt-Lys-Phe-NH_2 • First-in-Class

Evidence base at a glance: Unlike most mitochondrial peptides, SS-31 has substantial HUMAN data and is FDA-approved (FORZINITY, Sept 2025) for Barth syndrome. It is the first-in-class, first FDA-approved mitochondria-targeted therapeutic. All non-Barth uses remain off-label and investigational.

1. Peptide Profile

Common name: SS-31 / Elamipretide
Classification: Synthetic, mitochondria-targeted tetrapeptide; first-in-class cardiolipin-directed therapeutic
Sequence: D-Arg-Dmt-Lys-Phe-NH_2 (MW ≈ 639.8 g/mol)
Net charge: +3 at physiological pH
Aliases: Elamipretide, Bendavia, MTP-131; brand name FORZINITY
Mechanistic target: Cardiolipin on the inner mitochondrial membrane (IMM)
FDA status: Accelerated approval September 2025 for Barth syndrome (≥30 kg body weight)
FDA designations: Orphan Drug, Fast Track, Priority Review, Rare Pediatric Disease

Key Structural Features

- **Alternating cationic and aromatic residues:** the D-Arg/Lys cations and Dmt/Phe aromatics together make it cell-permeable and water-soluble
- **Peptidase resistance:** the D-amino acid and modified residues resist enzymatic degradation, aiding delivery into the cytoplasm and mitochondria
- **Selective for dysfunction:** normalizes OXPHOS in damaged mitochondria with essentially no effect on healthy mitochondria

2. Modes of Action & Mechanisms

SS-31 works fundamentally differently from electron carriers like CoQ10 or MitoQ. It does not add antioxidant capacity quantitatively; instead it binds cardiolipin and functionally restores the architecture of the inner membrane so that electron transport supercomplexes can reassemble and operate efficiently.

Cardiolipin Binding (the core mechanism)

- Binds cardiolipin via electrostatic (D-Arg, Lys) and hydrophobic (Dmt, Phe) interactions
- Accumulates ~5000-fold in mitochondria; concentrates at the IMM and is NOT transported into the matrix
- Stabilizes cristae membrane integrity and restores mitochondrial membrane potential
- Inhibits cytochrome c peroxidase activity and prevents cardiolipin peroxidation
- Modulates membrane surface electrostatics and divalent cation (Ca^{2+}) distribution at the inner surface

Electron Transport & ATP Synthesis

- Improves electron flow through Complexes I–IV by stabilizing ETC supercomplexes
- Enhances Complex IV activity specifically within supercomplex assemblies
- Interacts directly with the adenine nucleotide translocator (ANT) and ATP synthase, improving ADP sensitivity in aged mitochondria
- Reduces proton and electron leak — which lowers ROS generation at the source
- Inhibits opening of the mitochondrial permeability transition pore (mPTP)

Downstream Pathway Integration

Pathway	Effect
ROS / Nrf2 / NF-κB	Cuts mitochondrial ROS at the source; activates the Nrf2 antioxidant response; inhibits the master inflammatory regulator NF-κB
SIRT1 / SIRT3	Combined with other mito therapy, raises SIRT1/SIRT3 — suppressing inflammation and protecting mitochondrial integrity
Ferroptosis / GPX4	Activates mitochondrial glutathione/GPX4; clears ferrous iron and limits lipid peroxidation, alleviating mitochondria-dependent ferroptosis (Fenton-driven cell death)

Key conceptual point: cardiolipin amounts are UNCHANGED after treatment. The benefit is functional remodeling — reconnecting complexes to cardiolipin at the inner membrane so supercomplexes can form — not a quantitative restoration of cardiolipin.

3. Points of Clinical Relevance

1. **First FDA-approved mitochondria-targeted therapeutic — a category milestone**
   SS-31's accelerated approval for Barth syndrome makes it the first drug of its kind, validating cardiolipin as a druggable target and giving clinicians a genuine approved reference point that most other mitochondrial peptides lack.
2. **Selectivity for dysfunctional mitochondria is a major safety advantage**
   Because it normalizes OXPHOS only where mitochondria are impaired and leaves healthy mitochondria unaffected, the risk profile differs favorably from non-selective agents like CoQ10 and MitoQ, which act on normal and abnormal mitochondria alike.
3. **Effects are gradual and durable — set expectations accordingly**
   Functional cardiac benefits can take weeks to months to manifest (a 'gradual rebuilding' model), and meaningful residual benefit persists after stopping, well beyond the ~4-hour half-life. Patients should be counseled not to expect rapid change.
4. **Human efficacy is real but indication-dependent and mixed**
   The 168-week Barth open-label data (improved stroke volume, knee strength, 6-minute walk) supported approval, and a single dose reversibly improved ATP production in aging human muscle — yet the HFrEF trials (PREVIEW, PROGRESS-HF) did not meet primary endpoints. Benefit cannot be assumed across all mitochondrial diseases.
5. **100% renal excretion makes kidney function a dosing determinant**
   The peptide and its metabolites are entirely renally cleared, so baseline and ongoing renal function should be monitored and may influence dosing interval — particularly relevant in older or comorbid patients.
6. **Injection-site reactions are common but mild and manageable**
   Erythema (~57%) and pruritus (~47%) are the dominant adverse events, are generally mild and self-limiting, and can be managed with topical corticosteroids or oral antihistamines. No serious adverse events were reported across 168 weeks.
7. **Rational combinations target the broader bioenergetic network**
   Because SS-31 optimizes the ETC's use of NADH, it pairs mechanistically with NAD^+ precursors (NMN/NR), AMPK activators (metformin, berberine, GLP-1s) that drive mitochondrial biogenesis, and — in animal I/R models — exogenous mitochondrial transfer, which outperformed either intervention alone.

4. General Dosing & Delivery Options

FORZINITY (Barth syndrome) has an approved regimen. All other dosing below is from trials or evolving off-label practice and is presented for educational context only.

Approved & Trial Dosing

Setting	Route	Dose	Duration
FORZINITY (Barth, approved)	SC	40 mg/day	Continuous
TAZPOWER (Barth)	SC	40 mg/day	Up to 168 weeks
PREVIEW (HFrEF, Ph 1)	IV infusion	0.005–0.25 mg/kg/hr	Single 4-hour infusion
PROGRESS-HF (HFrEF, Ph 2)	SC	4 mg or 40 mg/day	28 days
Aging muscle (research)	SC	Single dose	Single administration
Preclinical (rodent)	IP	2–5 mg/kg/day	Varies (4–8 wks)

Evolving Off-Label Dosing Framework

For off-label, cardiolipin-focused use (age-related mitochondrial decline rather than Barth syndrome specifically), observed practice typically starts around 25 mg SC, up to a maximum of about 50 mg per sitting. Cycling is commonly twice weekly (e.g. Tuesday/Thursday), sometimes three times weekly, and occasionally — at lower doses — up to five times weekly, titrated to the severity of mitochondrial/cardiolipin dysfunction being addressed.

Pharmacokinetics

Absorption: Rapid after SC — peak plasma ~15 min, steady state ~30 min
Uptake: Not membrane-potential dependent; not receptor- or transporter-mediated (unsaturated absorption)
Excretion: 100% renal — peptide and metabolites detected in urine
Half-life: ~4 hours, but functional cardiac effects persist ~7 days after a single dose (animal data)
Concentration: ~1000-fold enrichment at the inner mitochondrial membrane via cardiolipin

Monitoring Markers (off-label use)

- Subjective improvement and fatigue indices
- Lactate:pyruvate and beta-hydroxybutyrate:acetoacetate ratios
- Functional strength measures (e.g. knee extensor strength) and cardiac parameters where relevant

5. Evidence Profile

Human Evidence

Study / Setting	Key Finding	Tier
TAZPOWER (Barth)	No effect on primary endpoints at 12 wks; 168-wk OLE: stroke volume +>45%, knee strength↑, 6MWT +96 m → basis for FDA approval	Phase 2/3 + OLE
PREVIEW (HFrEF)	Single 4-h IV: significant LVEDV/LVESV reduction at high dose; dose-effect correlation	Phase 1
PROGRESS-HF (HFrEF)	28-day SC: safe but primary LVESV endpoint NOT met	Phase 2
Aging muscle (Roshanravan)	Single SC dose reversibly raised mitochondrial ATP capacity — first in vivo reversal of mito dysfunction in aging human muscle	RCT
Ex vivo failing human heart	Improved Complex IV activity & respiratory control in failing tissue; no effect on non-failing tissue	Ex Vivo Human

Preclinical Evidence (selected)

- **Cardiac:** canine HF model — normalized respiration, Ca^{2+} tolerance, SERCA2a, ATP synthesis; reduced hypertrophy. Barth mice — restored mitochondrial morphology and mitophagy
- **Renal:** protected renal mitochondria; reduced ROS, apoptosis, fibrosis across AKI/CKD models; inhibited Nox4 and preserved podocytes in diabetic kidney
- **Neuro:** attenuated glutamate/rotenone-induced neuronal death; improved recovery after spinal cord injury; protected cognition in aging models

Critical gaps & negative data: PROGRESS-HF missed its primary HFrEF endpoint, and preclinical HFpEF showed improved respiration WITHOUT functional benefit once disease was established. A confirmatory trial is required to maintain Barth approval. Long-term safety in non-Barth populations and optimal off-label dosing remain undefined.

6. Clinical Considerations

Contraindications

- **Hypersensitivity:** serious hypersensitivity to elamipretide or formulation components
- **Neonates:** benzyl alcohol toxicity risk — do not use formulations containing benzyl alcohol in neonates
- **Caution:** long-term safety in healthy populations is limited; do not stack indiscriminately with experimental compounds

Monitoring Parameters

- Injection-site monitoring for local reactions
- Baseline and follow-up renal function (100% renal excretion)
- Cardiac function assessment if used for cardiomyopathy
- Functional strength measures and mitochondrial biomarkers where available

Adverse Event Profile

Adverse Event	Frequency	Severity
Injection-site erythema	57%	Mild
Injection-site pruritus	47%	Mild
Injection-site pain	20%	Mild
Injection-site urticaria	20%	Mild
Injection-site irritation	10%	Mild
Systemic serious AEs	None reported	—
ECG / hemodynamic changes	None clinically significant	—

SS-31 vs Other Mitochondrial Approaches

Feature	SS-31 / Elamipretide	CoQ10	MitoQ
Target	Cardiolipin (IMM)	Complex I–III	Ubiquinone (matrix)
Mechanism	Stabilizes cristae & ETC supercomplexes	Electron carrier	ROS scavenger (matrix)
Mito accumulation	~5000-fold	Variable (oral)	100–1000-fold
FDA approved	Yes (Barth)	No (supplement)	No
Selectivity	Dysfunctional mito only	Non-selective	Non-selective

Regulatory Status

FORZINITY is FDA-approved ONLY for Barth syndrome (≥30 kg). Every other use — heart failure, aging, renal, neurological, skeletal muscle — is off-label by definition. Continued Barth approval is contingent on a required confirmatory trial.

7. Final Note

SS-31 stands apart from most peptides discussed in this series: it is an FDA-approved, first-in-class mitochondrial therapeutic with genuine human efficacy and safety data, not a purely preclinical research compound. Its cardiolipin-binding mechanism is mechanistically elegant — restoring the function of the inner membrane and its supercomplexes rather than simply adding antioxidant capacity — and its selectivity for dysfunctional mitochondria gives it a favorable theoretical safety margin.

That said, clinicians should hold two truths together. The approved indication is narrow (Barth syndrome), and the broader promise — heart failure, age-related mitochondrial decline, renal and neurological protection — rests on a mix of compelling mechanism, positive aging-muscle and ex-vivo data, and trials that did not always meet their primary endpoints. For off-label use, the honest framing is a gradual-rebuilding therapy with durable effects, applied to a cardiolipin/oxidative-stress problem, monitored objectively and subjectively, within an evidence-based dosing framework that is still maturing.

Bottom line: The most clinically validated mitochondrial peptide available — FDA-approved for Barth syndrome, mechanistically selective, gradual and durable in effect. Beyond Barth, mechanistically promising but off-label, with mixed trial results and dosing still being defined.

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