

RESEARCH MONOGRAPH . COMPOUND PROFILE

SkQ1

A rechargeable, mitochondria-accumulating plastoquinone derivative developed at Lomonosov Moscow State University as a direct scavenger of reactive oxygen species at the inner mitochondrial membrane, with preclinical geroprotective, cytoprotective, and anti-inflammatory activity across multiple organ systems and a registered ophthalmic formulation (Visomitin) for dry eye syndrome.

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ABSTRACT

SkQ1 (10-(6'-plastoquinonyl)decyltriphenylphosphonium), designated a "Skulachev ion" after its principal developer Vladimir P. Skulachev, is a synthetic mitochondria-targeted antioxidant composed of a plastoquinone moiety linked by a ten-carbon aliphatic chain to a triphenylphosphonium cation. The triphenylphosphonium group exploits the large negative-inside mitochondrial membrane potential (approximately 180 millivolts) to drive electrophoretic accumulation of the compound within the mitochondrial matrix at concentrations estimated to reach 10(8)-fold above extracellular levels. Within the inner mitochondrial membrane, the plastoquinone headgroup intercalates near the cardiolipin fatty acid chains and directly quenches peroxy radicals, with regeneration of the reduced (antioxidant-active) form by Complex I at the IQ site and by Complex III at the Qi site of the electron transport chain. This rechargeable antioxidant cycle distinguishes SkQ1 from stoichiometric scavengers and positions it as a catalytic antioxidant with sustained activity at nanomolar external concentrations. The compound was developed beginning in the early 2000s at the A. N. Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, within a research framework centered on Skulachev's hypothesis that aging represents a form of programmed organismal death (phenoptosis) mediated by mitochondrial reactive oxygen species (mtROS). Preclinical studies in organisms spanning fungi (*Podospora anserina*), crustaceans (*Ceriodaphnia affinis*), insects (*Drosophila melanogaster*), fish (*Nothobranchius furzeri*), and mammals (mice and rats) have demonstrated lifespan extension, delay or reversal of age-related pathologies, and

suppression of mtROS-driven tissue damage under a variety of experimental conditions. In the senescence-accelerated OXYS rat strain, SkQ1 prevented or reversed cataracts, retinopathy resembling age-related macular degeneration, osteoporosis, and neurodegenerative phenotypes resembling Alzheimer's disease. In outbred and inbred mouse strains, SkQ1 extended median and maximum lifespan under non-specific-pathogen-free housing conditions, with effect sizes dependent on ambient pathogen exposure. The compound prevented rapid death caused by mechanistically diverse acute shocks including bacterial lipopolysaccharide, intravenous mitochondrial injection, cold exposure, and toxic insult. The ophthalmic formulation of SkQ1 (Visomitin, 0.155 micrograms per milliliter ophthalmic solution) was approved by the Russian Ministry of Health in December 2011 for the treatment of dry eye syndrome and early cataracts. In the United States, Mitotech S.A. advanced SkQ1 ophthalmic solution through a positive Phase 2 clinical trial demonstrating statistically significant improvement in corneal fluorescein staining and lissamine green staining relative to placebo in 91 subjects with mild to moderate dry eye disease. Two subsequent Phase 3 studies (VISTA-1, 452 subjects; VISTA-2, 610 subjects) did not meet their co-primary endpoints, although VISTA-2 demonstrated statistically significant superiority in a pre-specified secondary endpoint of central corneal fluorescein staining change in a Schirmer's score-defined subpopulation. Phase 1 oral formulation studies were conducted in Russia in 2016. Preclinical pharmacology extends beyond ophthalmology to include cardioprotection (hemorrhagic shock, doxorubicin-induced cardiomyopathy), nephroprotection (cisplatin-induced and ischemia-reperfusion acute kidney injury with ferroptosis inhibition), neuroprotection (stroke, Alzheimer's disease models in

OXYs rats), hepatoprotection, suppression of experimental colitis and autoimmune arthritis, wound healing acceleration, tumor growth inhibition in fibrosarcoma and rhabdomyosarcoma models, and antibacterial activity at micromolar concentrations. Safety pharmacology in rats and dogs has demonstrated a wide therapeutic window with no adverse effects on the central nervous system, cardiovascular system, or respiratory system at doses orders of magnitude above the efficacious range. The compound does not induce hepatic cytochrome P450 enzymes. This monograph reviews the chemistry, structural pharmacology, and rechargeable antioxidant mechanism of SkQ1; the comprehensive preclinical evidence across geroprotective, cytoprotective, and anti-inflammatory applications; the clinical evidence base in dry eye disease; the pharmacokinetic characteristics; sourcing and quality considerations; reconstitution and handling protocols; stack-interaction implications; the adverse-event and safety profile; and a structured comparative assessment of five mitochondria-targeted antioxidant candidates against SkQ1 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

Recommended name: SkQ1.

Full chemical name: 10-(6'-Plastoquinonyl)decyltriphenylphosphonium bromide.

Marketed name: Visomitin (Mitotech S.A.; Russian Federation, approved December 2011 for dry eye syndrome and early cataracts).

Development codes: SkQ1 (Skulachev ion Q1), PDTP (plastoquinonyl decyltriphenylphosphonium). The "Sk" designation refers to "Skulachev ion," a term coined to describe penetrating cations that accumulate electrophoretically in mitochondria, first described by Skulachev in 1969 and subsequently applied to this class of mitochondria-targeted compounds [1].

Chemical Abstracts Service registry number: 934826-68-3 (bromide salt). The bromide counterion is the standard supplied form for research and pharmaceutical applications.

International Union of Pure and Applied Chemistry name: [10-(4,5-dimethyl-3,6-dioxo-1,4-cyclohexadien-1-yl)decyl]triphenylphosphonium bromide.

PubChem compound identifier: 16679091 (SKQ-1 bromide).

1.2 Structural class and chemistry

SkQ1 belongs to the class of mitochondria-targeted antioxidants, a group of synthetic compounds composed of a lipophilic penetrating cation conjugated via an aliphatic linker to a redox-active (antioxidant) moiety. The structural design exploits the large negative-inside electrical potential of the inner mitochondrial membrane (approximately 180 millivolts) to drive electrophoretic accumulation of the cationic compound within the mitochondrial matrix at concentration ratios estimated at 10(3) to 10(4) per membrane traversed [2, 3].

The compound consists of three structural elements: (a) a plastoquinone head-group (2,3-dimethyl-1,4-benzoquinone, the quinone moiety of plant plastoquinone-9 found in chloroplast thylakoid membranes); (b) a saturated decyl (ten-carbon) aliphatic linker; and (c) a triphenylphosphonium (TPP⁺) cation. The ten-carbon linker length was selected from a structure-activity series as optimal for positioning the plastoquinone residue near carbon 9 or carbon 13 of cardiolipin fatty acid chains within the inner mitochondrial membrane, thereby maximizing interception of lipid peroxyl radicals at the site of cardiolipin peroxidation [3, 4].

Molecular formula: C₃₆H₄₂BrO₂P (bromide salt).

Molecular weight: 617.6 g/mol (bromide salt). The cation mass (without bromide counterion) is approximately 537.7 g/mol.

Physical properties: Yellow to brown waxy or sticky solid. Highly hygroscopic. Soluble in ethanol, dimethyl sulfoxide, and ethanol-water mixtures. Sparingly soluble in pure water. Ultraviolet absorption maxima at 225 nm and 261 nm (ethanol).

Stereochemistry: SkQ1 does not contain a stereocenter. The plastoquinone ring and decyl chain are achiral. No enantiomeric considerations apply to sourcing or quality verification.

1.3 Synthesis

The synthesis of SkQ1 proceeds through conjugation of a plastoquinone-bearing alkyl halide intermediate with triphenylphosphine. The general synthetic route involves: (a) preparation or acquisition of 2,3-dimethyl-1,4-benzoquinone (plastoquinone-0); (b) alkylation at the 6-position of the quinone ring with a ten-carbon omega-haloalkyl chain (typically 1,10-dibromodecane) under basic or radical-initiated conditions to yield 6-(10-bromodecyl)-2,3-dimethyl-1,4-benzoquinone; and (c) quaternization of triphenylphosphine with the terminal bromide of the alkyl chain to yield the triphenylphosphonium salt [3, 5]. The product is purified by column chromatography (silica gel, chloroform-methanol gradient) and characterized by nuclear magnetic resonance spectroscopy (¹H and ³¹P), mass spectrometry, and high-performance liquid chromatography. Industrial-scale synthesis has been conducted at multiple contract manufacturers for the Mitotech clinical supply chain. The compound is stored under nitrogen or argon atmosphere due to its hygroscopic nature and susceptibility to aerial oxidation of the quinone headgroup under prolonged ambient exposure.

2. Abstract

SkQ1 (10-(6'-plastoquinonyl)decyltriphenylphosphonium) is a mitochondria-targeted, rechargeable antioxidant developed at Lomonosov Moscow State University under the direction of Vladimir P. Skulachev as a pharmacological tool for testing the hypothesis that aging is a form of programmed organismal death (phenoptosis) driven by mitochondrial reactive oxygen species [1, 2]. The compound accumulates selectively in the mitochondrial matrix at concentrations orders of magnitude above the extracellular space, intercalates into the inner mitochondrial membrane near cardiolipin, and quenches lipid peroxyl radicals. The oxidized form is regenerated to the active reduced form by the mitochondrial electron transport chain at Complex I and Complex III, establishing a catalytic antioxidant cycle that sustains activity at nanomolar external concentrations [3, 4].

The preclinical pharmacology of SkQ1 is exceptionally broad. Lifespan extension has been demonstrated in fungi, crustaceans, insects, fish, and rodents [6, 7]. In the senescence-accelerated OXYS rat, SkQ1 prevented or reversed cataracts, retinopathy resembling age-related macular degeneration, and neurodegenerative changes [8, 9, 10]. In standard laboratory rodents, SkQ1 has demonstrated cardioprotection against hemorrhagic shock and doxorubicin injury, nephroprotection against cisplatin-induced and ischemia-reperfusion acute kidney injury (with a ferroptosis-inhibiting mechanism), neuroprotection in stroke models, suppression of experimental colitis and autoimmune arthritis, acceleration of dermal wound healing, inhibition of fibrosarcoma and rhabdomyosarcoma growth, and antibacterial activity [11, 12, 13, 14, 15, 16, 17, 18]. The compound prevented rapid animal death from mechanistically diverse shocks including lipopolysaccharide, intravenous mitochondrial injection, cold exposure, and toxic insult [19].

The ophthalmic formulation (Visomitin, 0.155 micrograms per milliliter) was approved in the Russian Federation in December 2011 for dry eye syndrome and early cataracts [20]. A multicenter Russian clinical trial in 240 patients with dry eye syndrome demonstrated statistically significant improvements in corneal fluorescein staining, tear break-up time, and Schirmer's test scores relative to placebo [20]. In the United States, a Phase 2 clinical trial in 91 subjects with mild to moderate dry eye disease demonstrated statistically significant improvement in corneal and conjunctival staining endpoints [21]. Two Phase 3 studies (VISTA-1 and VISTA-2) did not

meet their co-primary endpoints, although VISTA-2 showed significant improvement in a pre-specified secondary endpoint in a subpopulation defined by low Schirmer's scores [22]. Phase 1 oral formulation studies were conducted in Russia in 2016. The compound is not approved in the United States or in the European Union.

Efficacious doses of SkQ1 in preclinical models are characteristically low, in the range of 0.25 to 1.25 nanomoles per kilogram per day orally (approximately 0.13 to 0.7 micrograms per kilogram per day), reflecting the extreme mitochondrial accumulation [14]. The compound exhibits a wide therapeutic window with a 1000-fold separation between antioxidant concentrations (approximately 1 nanomolar) and prooxidant concentrations (approximately 1 micromolar), substantially wider than the 2- to 5-fold window reported for the structurally related compound MitoQ [3, 4]. Safety pharmacology studies in rats and dogs have demonstrated no adverse effects on the central nervous system, cardiovascular system, or respiratory system at doses far exceeding the efficacious range [21].

This monograph documents the chemistry, rechargeable antioxidant mechanism, comprehensive preclinical pharmacology, clinical evidence in dry eye disease, pharmacokinetics, sourcing and quality considerations, reconstitution and handling, stack interactions, adverse-event profile, and a comparative assessment of five mitochondria-targeted antioxidant candidates (MitoQ, MitoTEMPO, SS-31/elamipretide, plastoquinone-0, and idebenone) against SkQ1 on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Intellectual origins

The development of SkQ1 is rooted in two converging lines of investigation led by Vladimir P. Skulachev at the A. N. Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow. The first is the bioenergetics of penetrating ions. In 1969, Skulachev and colleagues demonstrated that lipophilic cations such as tetraphenylphosphonium and triphenylmethylphosphonium accumulate electrophoretically across biological membranes in response to transmembrane electrical potential, providing both a method for measuring mitochondrial membrane potential and a general targeting strategy for delivering payloads to the mitochondrial matrix [1]. These penetrating cations were subsequently termed "Skulachev ions" in the bioenergetics literature.

The second intellectual origin is the mitochondrial free radical theory of aging, extended by Skulachev into the concept of phenoptosis: the hypothesis that aging is not passive entropic decay but an active, genetically programmed process of organismal self-destruction analogous to apoptosis (programmed cell death), with mitochondrial reactive oxygen species serving as the executioner signal [23, 24]. Skulachev proposed in 1997 that if aging is mediated by mtROS, then a compound capable of specifically quenching mtROS at their site of production (the inner mitochondrial membrane) should retard or reverse the aging program.

3.2 Design and synthesis

The convergence of these ideas led to the design of SkQ1 in the early 2000s. The compound was synthesized by conjugating plastoquinone (the quinone electron carrier of plant chloroplast photosynthetic membranes) to a decyl-triphenylphosphonium cation. The choice of plastoquinone rather than ubiquinone (the quinone used in the structurally related MitoQ developed by Murphy and Smith at the University of Otago and MRC Dunn Human Nutrition Unit) was deliberate: plastoquinone demonstrated higher antioxidant efficiency in lipid bilayer peroxidation assays and, critically, a much wider separation between its antioxidant and prooxidant concentration ranges (approximately 1000-fold for SkQ1 versus 2- to 5-fold for

MitoQ) [3, 4]. The ten-carbon linker length was optimized from a series of analogs (SkQ3 with a shorter linker, SkQR1 with a rhodamine-based cation) to maximize membrane partitioning and antioxidant efficiency while maintaining aqueous solubility sufficient for pharmaceutical formulation.

3.3 The Skulachev Project

In 2005, Skulachev organized a large-scale collaborative research initiative (the "Skulachev Project") involving multiple research groups at Moscow State University and affiliated institutions in Russia, Sweden, the United States, and other countries. The project systematically evaluated SkQ1 in organisms spanning the tree of life. The landmark 2008-2009 publication "An attempt to prevent senescence: a mitochondrial approach" in *Biochimica et Biophysica Acta* summarized the first comprehensive results, demonstrating lifespan extension in *Podospora anserina*, *Ceriodaphnia affinis*, *Drosophila melanogaster*, and mice, and prevention of age-related pathologies in OXYS rats [4, 6].

3.4 Pharmaceutical development

Mitotech S.A. (Luxembourg, with research operations in Moscow) was established as the commercial development entity. The first pharmaceutical product, Visomitin ophthalmic solution (0.155 micrograms per milliliter SkQ1 in phosphate-buffered saline with hydroxypropyl methylcellulose), was developed for dry eye syndrome on the basis of the preclinical ophthalmologic data in OXYS rats and in rabbit models of uveitis and glaucoma [8, 9]. The Russian Ministry of Health approved Visomitin in December 2011. Mitotech subsequently initiated United States clinical development, completing a Phase 2 dry eye trial (published 2016) and two Phase 3 trials (VISTA-1 and VISTA-2, completed 2021) [21, 22]. An oral systemic formulation entered Phase 1 clinical testing in Russia in 2016. Cosmetic formulations (Mitovitan) and veterinary ophthalmic formulations have been marketed in Russia and selected other jurisdictions.

3.5 Patent landscape

SkQ1 and related Skulachev ion compounds are protected by patents granted in the Russian Federation, United States, China, Japan, and the European Union, covering composition of matter, methods of use in age-related diseases, and ophthalmic for-

mulations. The patents are assigned to Mitotech S.A. and to Lomonosov Moscow State University.

4. Mechanism of Action

SkQ1 is a mitochondria-targeted, rechargeable antioxidant. Its mechanism of action operates through three integrated steps: electrophoretic mitochondrial accumulation, direct radical scavenging at the inner mitochondrial membrane, and enzymatic regeneration of the active reduced form by the electron transport chain.

4.1 Mitochondrial accumulation

The triphenylphosphonium cation of SkQ1 carries a single positive charge delocalized across three phenyl rings and the phosphorus center. This charge delocalization creates a large, lipophilic cation that crosses lipid bilayer membranes readily. The Nernst equation predicts approximately 10-fold accumulation across a membrane for each 60 millivolts of negative-inside potential. The plasma membrane potential (approximately 60 millivolts negative inside) drives approximately 5- to 10-fold cytosolic accumulation; the mitochondrial membrane potential (approximately 180 millivolts negative inside) drives a further approximately 1000-fold accumulation into the matrix, yielding a total matrix-to-extracellular concentration ratio on the order of 10^3 to 10^4 [2, 3]. Under physiological conditions in cells containing numerous mitochondria with maintained membrane potential, total intracellular accumulation can approach 10^8 -fold at equilibrium.

4.2 Inner membrane intercalation and radical scavenging

Within the mitochondria, the amphiphilic SkQ1 molecule partitions into the inner mitochondrial membrane with the plastoquinone headgroup oriented toward the membrane interior and the triphenylphosphonium group anchored at the matrix-facing leaflet [3, 4]. The ten-carbon linker positions the plastoquinone near carbon 9 or carbon 13 of cardiolipin fatty acid chains. Cardiolipin (diphosphatidylglycerol) is a phospholipid unique to the inner mitochondrial membrane that is essential for the structural and functional integrity of respiratory chain supercomplexes and that is preferentially susceptible to peroxidation by superoxide-derived radicals owing to its high unsaturated fatty acid content.

The reduced form of SkQ1 (SkQ1H₂, the plastoquinol) directly reacts with lipid peroxyl radicals (LOO $\cdot$) and alkoxyl radicals (LO $\cdot$) by hydrogen atom transfer, interrupting the lipid peroxidation chain reaction. The reaction kinetics are comparable to those of alpha-tocopherol (vitamin E) in model membrane systems, with rate constants on the order of 10⁵ M⁻¹ s⁻¹ [3]. The scavenging activity is particularly effective against cardiolipin peroxidation owing to the positional proximity established by the linker length.

4.3 Rechargeable antioxidant cycle

A critical distinction between SkQ1 and stoichiometric antioxidants (such as alpha-tocopherol, which must be regenerated by ascorbate or other reductants) is the regeneration of the active plastoquinol form by the mitochondrial electron transport chain itself. The oxidized plastoquinone form of SkQ1, produced after radical scavenging, is reduced back to the plastoquinol by accepting electrons from Complex I at the IQ ubiquinone-binding site and from Complex III at the Q_i site [3, 25]. Both reductions simultaneously attenuate electron diversion to oxygen at these sites, thereby reducing superoxide formation. The compound therefore operates as a catalytic, self-regenerating antioxidant rather than a consumed scavenger, sustaining activity at nanomolar external concentrations over extended periods.

4.4 Additional mechanistic activities

Beyond direct radical scavenging, SkQ1 produces several secondary mechanistic effects:

Mild uncoupling. At concentrations above the primary antioxidant range, SkQ1 acts as a mild protonophore (uncoupler), reducing the mitochondrial membrane potential by a few millivolts. This mild uncoupling decreases the thermodynamic driving force for electron leak to oxygen at Complexes I and III, reducing basal superoxide production independently of the radical-scavenging mechanism [3].

Anti-inflammatory signaling. SkQ1 suppresses NF-kappaB-driven proinflammatory cytokine expression (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6, and ICAM-1) in multiple tissue models, consistent with the established role of mtROS as an activating signal for the NLRP3 inflammasome and NF-kappaB pathway [15, 16].

Ferroptosis inhibition. In models of acute kidney injury, SkQ1 prevented cell death through inhibition of ferroptosis, the iron-dependent form of regulated necrosis driven by lipid peroxidation [13]. The anti-ferroptotic mechanism is a direct consequence of the lipid peroxy radical scavenging activity at the mitochondrial membrane.

Cardiolipin preservation. By preventing cardiolipin peroxidation, SkQ1 preserves the structural integrity of respiratory chain supercomplexes and prevents cytochrome c release from the inner membrane, thereby suppressing the mitochondrial (intrinsic) apoptotic pathway [3, 4].

4.5 Therapeutic window

The antioxidant effect of SkQ1 is observed at external (extracellular) concentrations in the low nanomolar range (approximately 1 to 20 nanomolar). At external concentrations approaching 1 micromolar, the accumulated intramitochondrial concentration is sufficient to produce prooxidant effects (electron shuttling and radical generation from the reduced form). The ratio between antioxidant and prooxidant thresholds is approximately 1000-fold, substantially wider than the approximately 2- to 5-fold ratio for MitoQ and wider than the ratios for most other mitochondria-targeted redox agents [3, 4]. This wide therapeutic window is attributed to the more favorable redox potential of plastoquinone relative to ubiquinone in the membrane environment.

5. Pharmacokinetics and Routes of Administration

5.1 Mitochondrial pharmacokinetics

The pharmacokinetics of SkQ1 are dominated by its mitochondrial accumulation behavior rather than by classical plasma pharmacokinetic parameters. The Nernst-driven accumulation produces intramitochondrial concentrations that exceed plasma concentrations by orders of magnitude, and the effective pharmacodynamic half-life is determined by the rate of mitochondrial turnover and membrane potential decay rather than by plasma clearance [2, 3].

5.2 Ophthalmic pharmacokinetics

The primary characterized route of administration is topical ophthalmic. The Visomitin formulation delivers SkQ1 at 0.155 micrograms per milliliter (approximately 0.25 nanomolar), instilled as one to two drops per eye one to three times daily. Ocular bioavailability data from rabbit pharmacokinetic studies indicate corneal penetration with detectable concentrations in the aqueous humor within 30 minutes of instillation. Systemic absorption from the ophthalmic route is minimal; plasma concentrations following topical ocular administration are below the limit of quantitation in most analytical assays [21].

5.3 Oral pharmacokinetics

Oral pharmacokinetic data in humans are limited to the Phase 1 study conducted in Russia in 2016, the results of which have not been published in a peer-reviewed forum as of monograph revision. In preclinical rodent studies, oral administration by gavage at doses of 0.25 to 1.25 nanomoles per kilogram per day (approximately 0.13 to 0.7 micrograms per kilogram per day) produced efficacious tissue concentrations as determined by pharmacodynamic biomarkers (reversal of oxidative stress markers, improvement in disease endpoints) [14]. Oral bioavailability in rats has been

characterized as moderate, with absorption from the gastrointestinal tract and first-pass hepatic clearance. The compound is lipophilic (estimated logP greater than 5 for the cation), favoring membrane partitioning and tissue distribution.

5.4 Metabolism

SkQ1 does not induce hepatic cytochrome P450 enzymes. A dedicated study in rats administered SkQ1 in drinking water at 2.5 micromoles per kilogram (approximately 10-fold the therapeutic dose) for five days showed no increase in the content of cytochrome P450 isoforms in liver microsomes, and no induction was observed in human hepatocyte cell culture at comparable concentrations [26]. Metabolic pathways for SkQ1 have not been comprehensively characterized in published literature; the compound is expected to undergo hepatic oxidative metabolism with excretion of metabolites in bile and urine based on the general pharmacokinetic behavior of triphenylphosphonium conjugates.

5.5 Distribution

The compound distributes widely to tissues with high mitochondrial density (heart, kidney, liver, brain, skeletal muscle, retina). Volume of distribution data from systemic pharmacokinetic studies in rodents indicate extensive tissue partitioning consistent with the mitochondrial accumulation mechanism. Central nervous system penetration has been inferred from the neuroprotective effects observed in stroke and neurodegenerative disease models, although formal blood-brain barrier penetration studies have not been published.

5.6 Routes of administration

Three routes have been studied: topical ophthalmic (the registered route for Visomitin), oral (the systemic route evaluated in Phase 1), and subcutaneous or intraperitoneal injection (the principal preclinical routes for systemic studies). Intravenous administration has been used in acute shock models. The compound has also been administered in drinking water for chronic rodent studies.

6. Preclinical Pharmacology

6.1 Geroprotective effects and lifespan extension

The foundational preclinical pharmacology of SkQ1 is its geroprotective (anti-aging) activity, demonstrated across organisms spanning multiple phyla.

Fungi. In *Podospora anserina*, a filamentous fungus with a defined replicative lifespan limited by mitochondrial dysfunction, SkQ1 extended lifespan [6].

Crustaceans. In *Ceriodaphnia affinis*, SkQ1 extended lifespan in a dose-dependent manner [6].

Insects. In *Drosophila melanogaster*, SkQ1 extended median lifespan [6].

Fish. In *Nothobranchius furzeri* (the African turquoise killifish, a vertebrate model for aging research with a natural lifespan of 4 to 6 months), SkQ1 extended lifespan [6].

Rodents. Effects of SkQ1 on lifespan in rodents have been characterized in outbred mice and in three strains of inbred mice under both low-pathogen (LP) and specific-pathogen-free (SPF) housing conditions in vivaria in St. Petersburg, Moscow, and Stockholm [7]. Lifespan extension was observed preferentially in animals housed under non-SPF conditions, where infection is a significant cause of death, consistent with the anti-inflammatory and cytoprotective mechanisms of the compound. Under SPF conditions, effects on lifespan were smaller or absent in some strains, suggesting that the geroprotective benefit is mediated in part through protection against infection-related and inflammation-related mortality rather than through extension of the intrinsic replicative aging program alone.

6.2 OXYS rat studies

The senescence-accelerated OXYS rat strain, developed at the Institute of Cytology and Genetics of the Russian Academy of Sciences in Novosibirsk, develops a complex of age-related pathologies at an accelerated rate, including cataracts, retinopa-

thy resembling age-related macular degeneration, osteoporosis, and neurodegenerative changes resembling Alzheimer's disease. This strain has been the principal mammalian model for SkQ1 pharmacology.

Cataracts. SkQ1 eye drops completely prevented cataract development in OXYS rats when administered beginning at a young age, and in some animals diminished pre-existing cataractous changes when administered after disease onset [8].

Retinopathy. SkQ1 prevented the development and caused regression of pre-existing signs of retinopathy in OXYS rats, with the therapeutic action linked to improvement of VEGF and PEDF gene expression and downregulation of aryl hydrocarbon receptor-dependent genes in the retina [9, 10]. Long-term treatment suppressed development of AMD-like pathology by reducing amyloid-beta accumulation and suppressing mTOR activity in the retina.

Thymic involution. SkQ1 inhibited age-dependent involution of the thymus in both normal Wistar rats and in senescence-prone OXYS rats [27].

Biomarker reversal. When started late in life, SkQ1 not only prevented age-related decline in multiple biomarkers but also significantly reversed pre-existing age-related changes, including restoration of hair quality, reversal of lordokyphosis, and improvement of behavioral activity scores [28].

6.3 Cardioprotection

SkQ1 decreased inflammation and preserved myocardial mitochondrial integrity following hemorrhagic shock in a rat model, reducing proinflammatory cytokine release and preventing mitochondrial swelling and cristae disorganization [11]. In H9c2 cardiomyoblasts exposed to doxorubicin, both SkQ1 and MitoQ provided cytoprotection, with SkQ1 showing comparable efficacy to MitoQ in co-treatment protocols [12].

6.4 Nephroprotection

SkQ1 ameliorated acute kidney injury in cisplatin-induced, ischemia-reperfusion, and folic acid-induced models, with attenuation of renal injury biomarkers, histological indices of tubular injury, and inflammatory infiltration [13]. The nephroprotective mechanism was linked to inhibition of ferroptosis through prevention of mitochondrial lipid peroxidation.

6.5 Neuroprotection

SkQ1 at nanomolar concentrations effectively reduced oxidative damage in models of cerebral ischemia, brain injury, and Alzheimer's disease-like neurodegeneration. In OXYS rats, SkQ1 prevented neuronal loss and synaptic damage resembling spontaneous Alzheimer's disease pathology [29].

6.6 Anti-inflammatory and immunomodulatory effects

SkQ1 prevented the development of clinical and histological changes in dextran sodium sulfate (DSS)-induced colitis in mice and reduced mRNA expression of proinflammatory molecules TNF, IL-6, IL-1beta, and ICAM-1 in the proximal colon [15]. In the rat model of autoimmune arthritis (collagen-induced arthritis), SkQ1 administered by gavage at doses of 0.25 to 1.25 nanomoles per kilogram per day reduced the severity of arthritic lesions [14]. SkQ1 inhibited leukotriene synthesis in human neutrophils, providing a mechanistic basis for its anti-inflammatory activity independent of the mtROS-scavenging pathway [16].

6.7 Wound healing

SkQ1 accelerated dermal wound healing in animal models by suppressing the negative effects of oxidative stress in the wound and by inducing differentiation of wound-edge keratinocytes and fibroblasts [17].

6.8 Tumor growth inhibition

SkQ1 suppressed the growth of fibrosarcoma HT1080 and rhabdomyosarcoma RD tumor cells in culture and inhibited tumor growth of RD in a xenograft nude mouse model [18]. The antitumor mechanism is attributed to selective toxicity of the mitochondria-targeted antioxidant to tumor cells with high mitochondrial membrane potential and elevated basal ROS production, a phenotype common to many cancer cell types. This finding is notable given the general expectation that antioxidants might promote tumor growth; the mitochondrial targeting appears to invert this relationship in certain tumor contexts.

6.9 Antibacterial activity

SkQ1 and related mitochondria-targeted antioxidants demonstrated highly effective antibacterial activity at micromolar concentrations, attributed to disruption of bacterial membrane potential and proton motive force [30].

6.10 Acute shock protection

SkQ1 prevented rapid animal death caused by four mechanistically diverse shocks: (a) bacterial lipopolysaccharide (LPS) shock (sepsis model), (b) intravenous injection of isolated mitochondria (sterile inflammation model), (c) cold shock, and (d) toxic shock from rhabdomyolysis [19]. Protection in all four models supports the interpretation that mtROS are a common executioner pathway for diverse forms of acute organismal death.

7. Clinical Evidence Base

7.1 Dry eye syndrome (Russian registration trial)

The multicenter, randomized, double-masked, placebo-controlled clinical study of Visomitin eye drops in patients with dry eye syndrome was conducted in Russia and enrolled 240 patients [20]. Patients received Visomitin (0.155 micrograms per milliliter SkQ1) or placebo eye drops three times daily for 28 days. The active treatment group demonstrated statistically significant improvements relative to placebo in corneal fluorescein staining score, tear break-up time, and Schirmer's test score. The study supported the Russian regulatory approval of Visomitin in December 2011.

7.2 United States Phase 2 dry eye trial

A single-center, randomized, double-masked, placebo-controlled Phase 2 trial enrolled 91 subjects with mild to moderate dry eye disease in the United States [21]. Subjects were randomized 1:1:1 to SkQ1 1.55 micrograms per milliliter, SkQ1 0.155 micrograms per milliliter, or placebo ophthalmic solution, instilled twice daily for 29 days. SkQ1 demonstrated statistically significant improvements compared to placebo in corneal fluorescein staining (total and central region), lissamine green staining in the central region, and lid margin redness. The higher dose (1.55 micrograms per milliliter) showed additional improvements in the Controlled Adverse Environment (CAE) challenge model. The compound was well tolerated with no treatment-related serious adverse events (Petrov et al., 2016, *Advances in Therapy*).

7.3 Phase 3 VISTA-1 and VISTA-2 trials

Two Phase 3 trials were conducted in the United States under Mitotech S.A. sponsorship [22].

VISTA-1 enrolled 452 subjects randomized 1:1:1 to low-dose Visomitin, high-dose Visomitin, or placebo. The co-primary endpoints (corneal fluorescein staining and patient-reported symptom score) were not met.

VISTA-2 enrolled 610 subjects randomized 1:1 to high-dose Visomitin or placebo. The co-primary endpoints were not met. However, Visomitin demonstrated statistically significant superiority in a key pre-specified secondary endpoint: change from baseline to Day 29 in central corneal fluorescein staining in a large subpopulation defined by Schirmer's score (a measure of tear production). The result was characterized as highly clinically relevant.

The Phase 3 outcomes indicate that SkQ1 ophthalmic solution produces a real, measurable improvement in corneal epithelial integrity, but the effect size is insufficient to meet the stringent co-primary endpoint structure of a United States registration trial in the broad dry eye disease population. The Schirmer's-defined subpopulation finding suggests that the compound may be most effective in aqueous-deficient dry eye, a mechanistically coherent subpopulation given the mitochondrial oxidative stress contribution to lacrimal gland dysfunction.

7.4 Oral systemic formulation

Phase 1 clinical testing of an oral SkQ1 formulation was conducted in Russia in 2016. Published results from this study are not available in the peer-reviewed literature as of monograph revision. The oral formulation is intended for systemic age-related disease indications.

7.5 Ocular inflammation and wound healing

A peer-reviewed analysis of the role of SkQ1 (Visomitin) in inflammation and wound healing of the ocular surface was published in *Ophthalmology and Therapy* (Zinovkin et al., 2019), summarizing the mechanistic basis for anti-inflammatory and pro-healing effects in the corneal and conjunctival epithelium [31].

7.6 Glaucoma

Preclinical studies in rabbits demonstrated that SkQ1 eye drops at 5 micromolar concentration (one drop daily) retarded the development of glaucoma [4]. A clinical study of SkQ1 ophthalmic solution in open-angle glaucoma was reported by Iomdina et al. in the Russian ophthalmology literature, demonstrating reversal of glaucomatous lesions in a rabbit model and supportive clinical observations [32]. The glaucoma indication has not been evaluated in a registered clinical trial.

8. Sourcing and Quality Verification

Research-grade SkQ1 (as the bromide salt) is supplied by multiple chemical and pharmaceutical research suppliers including Cayman Chemical (catalog number 19891), Aladdin Scientific, MedKoo Biosciences (supplied as 200 mg/mL solution in ethanol-water 1:1 v/v), BOC Sciences, and others. Purity is typically reported as greater than 96 to 98 percent by HPLC area normalization. Pricing is moderate for a specialty research chemical, typically in the range of \$100 to \$500 per 5 to 25 milligrams depending on supplier and quantity.

Pharmaceutical-grade SkQ1 (Visomitin ophthalmic solution, 0.155 micrograms per milliliter) is available as a prescription product in the Russian Federation. The pharmaceutical-grade material represents the highest quality standard with full regulatory characterization.

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

- High-performance liquid chromatography area-percent purity (target greater than 96 percent, ideally greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (expected [M]⁺ for the cation at m/z 537.3; expected [M+Br]⁻ or equivalent salt adducts)
- ¹H and ³¹P nuclear magnetic resonance spectroscopy for structural confirmation (the ³¹P chemical shift of the triphenylphosphonium is diagnostic)
- Ultraviolet-visible spectrophotometry (absorption maxima at 225 nm and 261 nm in ethanol)
- Karl Fischer titration or loss-on-drying analysis for residual water content (critical given the highly hygroscopic nature of the compound)
- Residual solvent analysis if the compound is supplied as a solution or if the synthesis involves volatile solvents

The compound is highly hygroscopic and susceptible to aerial oxidation. Investigators should handle SkQ1 under inert atmosphere (nitrogen or argon) and store the solid at minus 20 degrees Celsius in sealed, desiccated containers. Lot-to-

lot variability in water content and oxidation state has been observed in research-grade material; on-receipt analytical confirmation is appropriate for quantitative dose-response studies.

9. Reconstitution and Handling

SkQ1 bromide is soluble in dimethyl sulfoxide (DMSO), ethanol, and ethanol-water mixtures. It is sparingly soluble in pure water. For in vitro cell culture work, stock solutions are typically prepared at 1 to 10 millimolar in DMSO and stored in single-use aliquots at minus 80 degrees Celsius. Working concentrations for antioxidant studies are in the 1 to 100 nanomolar range; concentrations approaching 1 micromolar should be evaluated for prooxidant activity. The final DMSO concentration in cell culture medium should not exceed 0.1 percent (v/v).

For in vivo oral administration in rodents, SkQ1 has been administered dissolved in drinking water at concentrations calibrated to deliver 0.25 to 250 nanomoles per kilogram per day based on measured water consumption. For gavage studies, solutions in ethanol-water or in aqueous vehicles with appropriate solubilizing agents have been used.

For ophthalmic applications, the Visomitin formulation uses phosphate-buffered saline (pH 6.2, osmolality approximately 260 mOsm/kg) with hydroxypropyl methylcellulose as a viscosity-enhancing agent. The SkQ1 concentration in the approved formulation is 0.155 micrograms per milliliter (approximately 0.25 nanomolar). Higher concentrations (1.55 micrograms per milliliter) were evaluated in the United States Phase 2 trial.

Storage of the solid compound should be at minus 20 degrees Celsius under desiccation and inert atmosphere. Stock solutions in DMSO are stable at minus 80 degrees Celsius for at least 6 months; ethanol solutions are stable at minus 20 degrees Celsius for shorter periods. Aqueous solutions should be prepared fresh or stored at 2 to 8 degrees Celsius and used within 7 to 14 days. The compound is light-sensitive; amber vials or foil wrapping are recommended for solutions.

Freeze-thaw cycles should be minimized. Single-use aliquoting of stock solutions is strongly recommended for quantitative work, as the compound's hygroscopic nature and oxidation susceptibility can introduce variability with repeated freeze-thaw exposure.

10. Stack Interactions and Combinations

SkQ1 interacts with several drug classes and research compound categories through its mitochondrial accumulation mechanism and its redox activity. Investigators conducting research with SkQ1, especially in combination protocols, should consider:

Other mitochondria-targeted compounds. Concurrent use with MitoQ, MitoTEMPO, SS-31 (elamipretide), or other triphenylphosphonium-conjugated compounds produces additive mitochondrial accumulation. Because all TPP⁺-conjugated compounds compete for electrophoretic uptake driven by the same membrane potential gradient, co-administration may produce unpredictable distribution effects and potential saturation of the mitochondrial accumulation capacity. The combination has not been systematically evaluated for safety or efficacy. Competition at the Complex I IQ and Complex III Qi reduction sites could alter the regeneration kinetics of each compound.

Mitochondrial uncouplers. Compounds that dissipate the mitochondrial membrane potential (FCCP, CCCP, DNP, niclosamide at high doses) abolish the driving force for SkQ1 mitochondrial accumulation and would be expected to eliminate its antioxidant activity. Mild uncouplers that reduce membrane potential by small increments (including SkQ1 itself at higher concentrations) could reduce but not abolish accumulation.

Electron transport chain inhibitors. Inhibitors of Complex I (rotenone, metformin at high concentrations) or Complex III (antimycin A, myxothiazol) interfere with the regeneration of the reduced (antioxidant-active) plastoquinol form of SkQ1 by blocking electron transfer at the IQ and Qi sites, respectively. Concurrent use could convert SkQ1 from a rechargeable to a stoichiometric antioxidant, reducing its effective potency [25].

Conventional antioxidants. N-acetylcysteine, alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), and other non-targeted antioxidants operate in different cellular compartments (cytosol, extracellular space, membrane bulk phase) and are not expected to produce direct pharmacokinetic interactions with SkQ1. The

combination of SkQ1 with N-acetylcysteine has been directly compared; SkQ1 reversed aging-related biomarkers in rats whereas N-acetylcysteine did not, suggesting that mitochondrial targeting is critical and that the two compounds are not pharmacodynamically redundant [28].

Iron chelators. Given the ferroptosis-inhibiting mechanism of SkQ1 in acute kidney injury models, concurrent administration with iron chelators (deferioxamine, deferiprone, deferasirox) could produce additive anti-ferroptotic effects. The combination has potential research utility in ferroptosis-driven pathologies but has not been characterized for safety.

Cytochrome P450 substrates. SkQ1 does not induce hepatic cytochrome P450 enzymes at doses up to 10-fold the therapeutic range [26]. Drug-drug interactions mediated by CYP enzyme induction or inhibition are therefore unlikely, though comprehensive CYP inhibition studies have not been published.

QT-prolonging agents. No QT-prolongation signal has been reported for SkQ1 in preclinical cardiovascular safety studies in Beagle dogs [21]. Concurrent use with QT-prolonging agents is not expected to produce additive cardiac risk based on available data, but formal thorough QT studies in humans have not been published.

11. Adverse Events and Safety

11.1 Preclinical safety pharmacology

Comprehensive safety pharmacology studies have been conducted in rodents and dogs [21]. In rats administered SkQ1 orally at doses of 0, 5, 25, and 100 milligrams per kilogram, no adverse effects on general behavior, motor activity, or central nervous system function were observed. In Beagle dogs administered SkQ1 orally at doses of 0, 7.75, 77.5, and 775 micrograms per kilogram, no effects on cardiovascular parameters (blood pressure, heart rate, pulse pressure), electrocardiography (PR, QRS, QT, QTc intervals), body temperature, or clinical condition were observed.

11.2 Ocular safety

In a local tolerance study of acute eye irritation in rabbits, a single dose of Visomitin at 155 nanograms per milliliter (0.015 micrograms per eye) showed no ocular irritation. A 28-day repeat-dose ocular toxicity study in rabbits with a 14-day recovery period determined the following: 0.15 micrograms per eye three times daily showed no ocular irritation; 1.5 micrograms per eye three times daily represented the no-observed-adverse-effect-level (NOAEL) for ocular toxicity; 15 micrograms per eye three times daily showed mild ocular irritation and represented the NOAEL for systemic toxicity [21].

11.3 Clinical adverse events

In the United States Phase 2 dry eye trial (91 subjects, 29 days of dosing), SkQ1 ophthalmic solution was well tolerated [21]. No treatment-related serious adverse events were reported. Ocular adverse events (mild stinging on instillation, transient blurred vision) were infrequent and comparable to placebo. In the VISTA-1 and VISTA-2 Phase 3 trials (combined enrollment of over 1,000 subjects), the safety profile was consistent with the Phase 2 findings, with no clinically significant safety signals reported [22].

In the Russian multicenter trial (240 patients, 28 days of dosing), Visomitin was well tolerated with no treatment-related serious adverse events [20].

11.4 Therapeutic window considerations

The approximately 1000-fold separation between antioxidant and prooxidant concentrations provides a substantial safety margin for the compound [3, 4]. At the approved ophthalmic concentration (0.155 micrograms per milliliter, approximately 0.25 nanomolar), the delivered concentration is well within the antioxidant range and orders of magnitude below the prooxidant threshold. For systemic oral dosing, the efficacious preclinical dose range (0.13 to 0.7 micrograms per kilogram per day) is similarly well below the concentrations at which prooxidant effects have been observed in vitro or in vivo.

11.5 Mutagenicity and carcinogenicity

Published mutagenicity and carcinogenicity data specific to SkQ1 are limited. The compound has not been reported to produce genotoxic effects in standard in vitro assays (Ames test, chromosomal aberration assay). The tumor growth inhibition observed in fibrosarcoma and rhabdomyosarcoma models [18] and the absence of spontaneous carcinogenesis signal in lifetime rodent studies [7] argue against a carcinogenic liability, although definitive two-year carcinogenicity bioassay data have not been published.

11.6 Reproductive toxicity

Published reproductive and developmental toxicity data for SkQ1 are limited. Use in pregnancy and lactation is not recommended in the absence of adequate safety data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five mitochondria-targeted antioxidant or cytoprotective candidates against SkQ1, 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 the principal mitochondria-directed compounds with substantive clinical or advanced preclinical programs, with priority on those sharing SkQ1's mechanistic space.

12.1 MitoQ (mitoquinone mesylate)

Mechanism: Mitochondria-targeted antioxidant consisting of ubiquinone-10 (coenzyme Q10) conjugated via a ten-carbon aliphatic linker to a triphenylphosphonium cation. Structural analog of SkQ1 with ubiquinone replacing plastoquinone as the antioxidant moiety [33].

Development trajectory: Developed by Michael Murphy and Robin Smith at the MRC Dunn Human Nutrition Unit (Cambridge) and the University of Otago (New Zealand). MitoQ is marketed as a dietary supplement (not a pharmaceutical) through MitoQ Ltd. (New Zealand) and is widely commercially available. Clinical trials have been conducted in Parkinson's disease (Snow et al., 2010, a Phase 2 randomized double-blind placebo-controlled trial in 128 untreated Parkinson's patients; negative primary outcome), in hepatitis C virus-related liver disease (Gane et al., 2010; reduced alanine aminotransferase but no effect on viral load), and in vascular endothelial function in older adults (Rossman et al., 2018; improved flow-mediated dilation) [34, 35, 36].

Novelty: Moderate. MitoQ was the first mitochondria-targeted antioxidant to reach clinical testing and is the historical reference compound for the class. The concept is well established.

Effect size: Moderate in vascular function studies. The Parkinson's disease trial was negative. Preclinical effect sizes are comparable to SkQ1 in many models but with a narrower therapeutic window.

Promising potential: Moderate. The compound is commercially available as a supplement with broad consumer adoption. Pharmaceutical development has not progressed beyond Phase 2.

Side-effect profile: Generally well tolerated in clinical trials at oral doses of 40 to 80 milligrams per day. The principal concern is the narrow therapeutic window (approximately 2- to 5-fold between antioxidant and prooxidant concentrations), which limits dose escalation and produces dose-dependent prooxidant toxicity at concentrations achievable with aggressive dosing [3, 4].

Overall validation: Moderate to high. MitoQ has the largest clinical literature of any mitochondria-targeted antioxidant and is the most commercially successful, although as a supplement rather than a registered pharmaceutical. The negative Parkinson's trial is a significant clinical setback for the class.

Comparison to SkQ1: SkQ1 and MitoQ share the same targeting mechanism (TPP⁺ cation, ten-carbon linker) but differ in the antioxidant moiety (plastoquinone versus ubiquinone). SkQ1 has a substantially wider therapeutic window (1000-fold versus 2- to 5-fold), which is its principal pharmacological advantage. MitoQ has a larger commercial footprint, a broader clinical trial portfolio, and wider availability. SkQ1 has the advantage of a registered pharmaceutical product (Visomitin) with regulatory approval, whereas MitoQ is marketed only as a dietary supplement.

12.2 MitoTEMPO

Mechanism: Mitochondria-targeted superoxide dismutase mimetic consisting of the nitroxide radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) conjugated to a triphenylphosphonium cation. Unlike SkQ1 and MitoQ (which scavenge lipid peroxyl radicals), MitoTEMPO catalytically dismutates superoxide to hydrogen peroxide and oxygen [37].

Development trajectory: Research tool compound widely used in preclinical studies of mitochondrial oxidative stress. No clinical development program. Available from multiple research chemical suppliers (Sigma-Aldrich, Cayman Chemical, Tocris).

Novelty: Moderate. The superoxide dismutase mimetic mechanism is distinct from the quinone-based radical scavenging of SkQ1 and MitoQ, providing complementary mechanistic information.

Effect size: Substantial in preclinical models of hypertension, cardiac hypertrophy, diabetic cardiomyopathy, and endothelial dysfunction. A comparative study showed comparable efficiency to SkQ1 under oxidative stress conditions in certain assays [38].

Promising potential: Low as a clinical candidate (no clinical development). Substantial as a research tool for dissecting superoxide-specific versus lipid peroxyl radical-specific contributions to mitochondrial oxidative damage.

Side-effect profile: Preclinical only. No human safety data.

Overall validation: Low. The compound is principally a research tool.

Comparison to SkQ1: MitoTEMPO addresses a different reactive oxygen species (superoxide) through a different mechanism (catalytic dismutation) than SkQ1 (lipid peroxyl radical scavenging). The two compounds are mechanistically complementary and are frequently used together in research to dissect the relative contributions of superoxide versus lipid peroxidation to a given pathological phenotype. SkQ1 has the advantages of clinical development, a registered pharmaceutical product, and extensive in vivo geroprotective data that MitoTEMPO lacks.

12.3 SS-31 (elamipretide, Bendavia, MTP-131)

Mechanism: Mitochondria-targeted tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH₂) that binds selectively to cardiolipin in the inner mitochondrial membrane. SS-31 does not use the TPP⁺ cation targeting strategy; instead, it concentrates at the inner membrane through electrostatic interaction between its cationic arginine and lysine residues and the anionic cardiolipin headgroups. The mechanism involves stabilization of cytochrome c-cardiolipin interactions, preservation of mitochondrial cristae structure, and reduction of electron leak from respiratory chain supercomplexes [39].

Development trajectory: Developed by Hazel Szeto at Weill Cornell Medicine. Stealth BioTherapeutics advanced elamipretide through multiple clinical trials including Phase 3 trials in primary mitochondrial myopathy (MMPOWER-3; did not meet primary endpoint), Barth syndrome (TAZPOWER; improvement in six-minute walk test), and heart failure with preserved ejection fraction (Phase 2 positive signal). The compound received FDA Rare Pediatric Disease designation and Orphan Drug designation for Barth syndrome [40, 41].

Novelty: High. The cardiolipin-binding peptide mechanism is fundamentally distinct from the TPP+-quinone approach of SkQ1 and MitoQ. SS-31 targets the same organelle but through a different molecular interaction (protein-lipid binding versus electrophoretic accumulation).

Effect size: Phase 2 heart failure data showed meaningful improvement in cardiac function parameters. The MMPOWER-3 Phase 3 trial in primary mitochondrial myopathy was negative. Barth syndrome data were positive in a small orphan population.

Promising potential: Moderate to high. Elamipretide is the most clinically advanced mitochondria-targeted compound in development for systemic indications. The Barth syndrome data support continued development in rare mitochondrial diseases.

Side-effect profile: Generally well tolerated in clinical trials. Injection site reactions were the principal adverse event (elamipretide is administered subcutaneously). No serious systemic safety signals in Phase 2 and Phase 3 studies.

Overall validation: Moderate to high. The compound has produced the most extensive Phase 3 clinical dataset of any mitochondria-targeted agent, although with mixed efficacy results.

Comparison to SkQ1: SS-31 and SkQ1 both target mitochondria and both interact with cardiolipin, but through entirely different mechanisms (direct peptide-cardiolipin binding versus quinone intercalation near cardiolipin fatty acid chains). SS-31 has a more advanced systemic clinical development program. SkQ1 has a registered ophthalmic product and a broader preclinical geroprotective literature spanning multiple phyla. The two compounds are mechanistically distinct enough that combination research could be scientifically productive.

12.4 Plastoquinone-0 (2,3-dimethyl-1,4-benzoquinone)

Mechanism: The unconjugated plastoquinone moiety of SkQ1, without the TPP+ cation targeting group. Acts as a conventional (non-targeted) quinone antioxidant through stoichiometric radical scavenging in aqueous and membrane environments [3].

Development trajectory: Research tool compound. Not in clinical development. Available from standard chemical suppliers at low cost.

Novelty: Low. The compound is the parent quinone of SkQ1 and serves as a control to demonstrate the contribution of mitochondrial targeting to SkQ1's activity.

Effect size: Substantially lower than SkQ1 in all published comparative studies, typically requiring 100- to 1000-fold higher concentrations to achieve comparable antioxidant effects in cellular and animal models [3]. This differential directly quantifies the contribution of mitochondrial targeting.

Promising potential: None as a clinical candidate. Important as a research control.

Side-effect profile: Toxicity at high concentrations due to pro-oxidant quinone chemistry. No human safety data.

Overall validation: Low. The compound's principal scientific value is as a negative control for the mitochondrial targeting component of SkQ1.

Comparison to SkQ1: Plastoquinone-0 and SkQ1 share the same antioxidant headgroup. The difference in potency (100- to 1000-fold) directly demonstrates the quantitative contribution of mitochondrial targeting and the catalytic regeneration mechanism to SkQ1's efficacy. Plastoquinone-0 is not a practical alternative to SkQ1 for any research or clinical application.

12.5 Idebenone (CoQ10 short-chain analog)

Mechanism: Synthetic short-chain analog of coenzyme Q10 (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone). Acts as an electron carrier that can bypass deficient Complex I by transferring electrons directly to Complex III, and as an antioxidant through quinol-mediated radical scavenging. Not specifically mitochondria-targeted; distributes to all cellular membranes [42].

Development trajectory: Santhera Pharmaceuticals developed idebenone (Raxone/Catena) for Leber's hereditary optic neuropathy (LHON), Duchenne muscular dystrophy (DMD), and Friedreich's ataxia. Received conditional marketing authorization in the European Union for LHON in 2015 (the first treatment approved for this indication). Phase 3 trials in DMD (DELOS, SIDEROS) produced mixed results; the SIDEROS trial in DMD patients not receiving glucocorticoids did not meet its primary endpoint [42, 43].

Novelty: Low to moderate. The compound has been in clinical investigation since the 1980s and is a well-characterized quinone electron carrier.

Effect size: Clinically meaningful in LHON (visual acuity improvement in a subset of patients with discordant visual acuity). Modest to absent in DMD by the primary endpoints of the Phase 3 SIDEROS trial.

Promising potential: Moderate. Registered in the European Union for LHON. DMD development has stalled.

Side-effect profile: Generally well tolerated. Gastrointestinal effects (nausea, diarrhea) at high doses (up to 2250 mg/day in DMD trials). Chromaturia (orange discoloration of urine) is common and benign. No serious systemic safety concerns.

Overall validation: Moderate to high. The compound has a registered indication (LHON) and decades of clinical and preclinical data.

Comparison to SkQ1: Idebenone and SkQ1 operate through fundamentally different strategies. Idebenone is a non-targeted quinone electron carrier that compensates for Complex I deficiency by bypassing the deficient complex. SkQ1 is a mitochondria-targeted antioxidant that scavenges radicals at the inner membrane and is regenerated by the electron transport chain. Idebenone has an established regulatory pathway (EU-approved for LHON). SkQ1 has regulatory approval in Russia for dry eye and a broader geroprotective research portfolio. The two compounds are not pharmacologically redundant and could be considered for different research applications: idebenone for Complex I-deficient mitochondrial diseases, SkQ1 for mtROS-driven aging and inflammatory pathologies.

12.6 Comparator summary

The five compounds occupy distinct positions in the mitochondria-directed pharmacology space. **MitoQ** is the historical reference compound for the TPP+-quinone class, with the broadest commercial footprint but the narrowest therapeutic window and a negative Parkinson's disease Phase 2 trial. **MitoTEMPO** is a mechanistically complementary research tool (superoxide dismutase mimetic) without clinical development. **SS-31 (elamipretide)** represents the most novel approach (cardiolipin-binding peptide) with the most advanced systemic clinical development, including mixed Phase 3 results. **Plastoquinone-0** serves as a control compound

demonstrating the 100- to 1000-fold potency enhancement conferred by mitochondrial targeting. **Idebenone** is a non-targeted quinone electron carrier with EU regulatory approval for LHON and decades of clinical history.

SkQ1 occupies a distinctive position in this landscape: it is the only compound with a registered pharmaceutical product (Visomitin ophthalmic solution, Russian Federation), the only compound with a comprehensive geroprotective dataset spanning fungi through mammals, the compound with the widest documented therapeutic window (1000-fold) in its structural class, and the compound with the most extensive preclinical literature across age-related diseases. Its clinical trajectory in the United States has been limited by the negative Phase 3 dry eye outcomes, but the Phase 2 efficacy signal, the pre-specified subpopulation finding in VISTA-2, and the breadth of preclinical support across multiple organ systems support continued research interest.

The principal practical question for investigators is whether the mitochondria-targeted antioxidant approach can deliver clinical benefit in systemic age-related diseases. The MitoQ Parkinson's trial and the SS-31 MMPOWER-3 trial both failed to meet primary endpoints in neurodegenerative and mitochondrial disease populations, respectively, suggesting that the clinical translation of the preclinical mtROS-scavenging paradigm is more challenging than the animal data predict. SkQ1's wider therapeutic window and rechargeable mechanism may offer advantages over MitoQ in this translation, but definitive human systemic efficacy data are not yet available.

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