***Review***

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# Mitochondrial DNA A3243G variant-associated MELAS: Recent advances in clinical trials, therapeutic interventions, and disease-modifying strategies

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**SUMMARY**: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, most often caused by the m.3243A>G mitochondrial DNA variant, represents one of the most clinically significant inherited mitochondrial disorders. This variant disrupts mitochondrial tRNALeu(UUR) function, leading to impaired mitochondrial protein synthesis and progressive multisystem dysfunction. This narrative review synthesizes recent clinical trials, therapeutic advances, and emerging disease-modifying strategies for m.3243A>G-associated MELAS, with emphasis on evidence published between 2024 and 2026, drawing on PubMed/MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, and the EU Clinical Trials Register. Key advances include: *i*) regulatory approval of high-dose taurine supplementation (9–12 g/day), which achieved complete prevention of stroke-like episodes in 60% of participants in a phase III trial; *ii*) phase IIb data (company-reported) indicating that sonlicromanol (KH176) showed signals of improvement in cognition, mood, and fatigue, supporting progression to a phase III registrational trial (KHENERFIN, NCT06451757); *iii*) ongoing trials of zagociguat and TTI-0102 targeting vascular dysfunction and oxidative stress; *iv*) KL1333, a novel NAD+ modulator, in phase II evaluation (FALCON trial); and *v*) promising preclinical gene-based approaches—including mitochondria-targeted TALENs, DdCBE base editors, and mitoARCUS nucleases—demonstrating heteroplasmy shifting in patient-derived cells and animal models, though direct clinical applicability to m.3243A>G MELAS requires further investigation. The therapeutic landscape for MELAS is evolving from symptomatic care toward mechanism-based disease modification, led by taurine as the first regulatory-approved disease-modifying therapy and complemented by late-stage small molecules and mitochondrial genome-editing technologies.

***Keywords***: cysteamine, NAD, oxidative stress, genetic therapy, taurine

## 1. Introduction

### 1.1. Clinical significance of the m.3243A>G variant

Mitochondrial DNA (mtDNA) disorders comprise a heterogeneous group of inherited diseases that impair oxidative phosphorylation (OXPHOS), and the m.3243A>G transition in the *MT-TL1* gene is among the most prevalent and clinically important pathogenic variants (*1*). With an estimated population frequency of 7.6–236 per 100,000, the m.3243A>G variant accounts for approximately 80% of genetically confirmed MELAS cases and is the primary genetic cause of maternally inherited diabetes and deafness (MIDD) (*2,3*).

This variant disrupts the structure and function of mitochondrial $tRNA^{Leu(UUR)}$, specifically impairing post-transcriptional taurine modification at the wobble uridine base ($\tau m^5U$; 5-taurinomethyluridine) (*4*). The resulting defect compromises codon recognition and mitochondrial protein translation, leading to respiratory chain dysfunction that preferentially affects metabolically demanding tissues, including the central nervous system (CNS), cardiac muscle, and skeletal muscle (*5*).

### 1.2. Phenotypic spectrum and clinical burden

Clinical expression of m.3243A>G-related disease is highly heterogeneous, ranging from asymptomatic carriers to severe multisystem disease with early mortality (*6*). MELAS represents the most severe phenotype and is characterized by stroke-like episodes (reported in 95% of patients), seizures (88%), encephalopathy with cognitive

decline (90%), and lactic acidosis (85%) (*7*). These recurrent stroke-like episodes, which typically occur before age 40 years, cause cumulative neurologic injury and progressive disability (*8*).

In contrast, the MIDD phenotype has a more restricted but characteristic presentation, with diabetes mellitus affecting approximately 90% of patients and progressive sensorineural hearing loss affecting approximately 95% (*9,10*). Additional systemic manifestations observed across the MELAS–MIDD spectrum include cardiomyopathy (25%–30%), retinal dystrophy (45%–75%), nephropathy (25%–35%), and gastrointestinal dysfunction (*11,12*).

### 1.3. Evolution of treatment paradigms

Historically, management of MELAS largely focused on symptomatic care, including seizure control, metabolic support, and prevention of complications (*13*). Over the past decade, however, the field has shifted toward mechanism-based interventions that target key pathophysiologic pathways implicated in m.3243A>G disease. Major advances include *i*) identification of the taurine modification defect as a central pathogenic mechanism, enabling the development of targeted taurine supplementation (*14*); *ii*) recognition of nitric oxide (NO) deficiency and endothelial dysfunction in stroke-like episode pathogenesis, supporting L-arginine/L-citrulline-based approaches (*15*); *iii*) development of novel small-molecule therapeutics, including ROS-redox modulators (sonlicromanol), $NAD^+$ enhancers (KL1333), and soluble guanylate cyclase stimulators (zagociguat) (*16,17*); and *iv*) rapid progress in gene-based technologies designed to manipulate mitochondrial heteroplasmy using mitochondria-targeted nucleases and base editors (*18,19*).

In this review, I synthesize recent clinical trial data, therapeutic advances from 2024 to 2026, and emerging disease-modifying strategies for m.3243A>G-associated MELAS.

## 2. Review approach

### 2.1. Literature search and source selection

I conducted a comprehensive literature review of publications from January 2020 through February 2026, with an emphasis on developments reported in 2024–2026. I searched PubMed/MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, and the EU Clinical Trials Register (CTIS). Search terms included "MELAS syndrome," "mitochondrial encephalomyopathy," "m.3243A>G variant," "A3243G mutation," "*MT-TL1*," "taurine therapy," "L-arginine," "sonlicromanol," "KL1333," "zagociguat," "gene therapy," "mitoTALEN," "DdCBE," "clinical trials," and "heteroplasmy."

### 2.2. Scope and evidence selection

I included *i*) phase I–III clinical trials evaluating therapeutic interventions for MELAS; *ii*) observational studies reporting treatment outcomes in patients with genetically confirmed m.3243A>G; *iii*) preclinical studies of gene-based approaches providing proof of concept, particularly those using patient-derived cells and demonstrating functional rescue; *iv*) reviews and consensus statements relevant to MELAS management; and *v*) English-language publications.

I excluded *i*) case reports including fewer than three patients; *ii*) studies focused exclusively on mtDNA mutations other than m.3243A>G without extractable m.3243A>G-specific data; and *iii*) *in vitro* studies that did not include validation in patient-derived cells.

### 2.3. Data synthesis

For each clinical trial, I extracted study design, sample size, patient population, intervention details (agent, dose, and duration), primary and secondary endpoints, efficacy findings, safety outcomes, and registration identifiers. For preclinical gene-based studies, I extracted the technology platform, target mutation, model system, magnitude of heteroplasmy shift, and evidence of functional restoration.

### 2.4. Evidence appraisal

I appraised preclinical studies for translational relevance based on the use of patient-derived cells or tissues and demonstration of correction of a disease-relevant functional phenotype.

## 3. Current and emerging therapeutic strategies

### 3.1. Taurine supplementation: First regulatory-approved disease-modifying therapy

#### 3.1.1. Molecular rationale and mechanism

The discovery that the m.3243A>G variant disrupts taurine-dependent post-transcriptional modification at position 34 (the wobble position) of mt-$tRNA^{Leu(UUR)}$ identified a specific molecular target for therapy (*20*). In healthy mitochondria, this uridine is modified to 5-taurinomethyluridine ($\tau m^5U$), which is required for accurate decoding of UUG leucine codons; in m.3243A>G, $\tau m^5U$ hypomodification promotes mistranslation and destabilization of respiratory chain subunits (*21*).

Preclinical experiments using patient-derived cybrid cells showed that taurine supplementation (0.3 mM in culture media) improved oxygen consumption, restored mitochondrial membrane potential, and reduced oxidative stress (*22*), supporting proof of concept for targeting the taurine modification defect.

3.1.2. Phase III clinical trial data

A multicenter, open-label phase III trial by Ohsawa and colleagues enrolled 10 patients with recurrent stroke-like episodes and genetically confirmed m.3243A>G. Participants received high-dose taurine for 52 weeks: 9 g/day for body weight < 50 kg and 12 g/day for body weight ≥ 50 kg, administered in three divided doses with meals.

Primary endpoint findings included: *i*) Complete prevention of stroke-like episodes (100% responder rate): 60% (95% CI: 26.2%–87.8%); *ii*) The lower bound of the 95% CI (26.2%) exceeded the prespecified null threshold of 5%, supporting statistical significance.

Secondary endpoint findings included: *i*) ≥ 50% reduction in stroke-like episode frequency (50% responder rate): 80% (95% CI: 44.4%–97.5%); *ii*) Annual stroke-like episode relapse rate decreased from 2.22 ± 0.73 (pretrial) to 0.72 ± 0.62 during the evaluation period ($p = 0.001$); and *iii*) Annual focal neurologic deficit events decreased from 33 episodes (pretrial) to 8 episodes during the evaluation period.

Mechanistic validation was demonstrated by increased $\tau m^5U$ modification rates in peripheral blood leukocytes after treatment in five assessed patients ($p < 0.05$), indicating target engagement with oral taurine (*23*).

Safety findings indicated no severe adverse events attributed to taurine; long-term tolerability has been favorable, with preliminary observations of sustained benefit in patients treated for more than 9 years and no evidence of cumulative toxicity (*22*).

3.1.3. Regulatory status and implementation

Based on these results, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) granted marketing authorization for taurine to prevent stroke-like episodes in MELAS in February 2019, representing the first disease-modifying therapy to receive formal regulatory approval for MELAS (in Japan; approved as タウリン散98%「大正」 by Taisho Pharmaceutical Co., Ltd.; orphan drug designation; PMDA approval list: *https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0030.html*, accessed June 2026) (*24*). In clinical practice, the labeled approach is used for patients with genetically confirmed m.3243A>G and a history of recurrent stroke-like episodes, typically at 9–12 g/day divided three times daily with meals, with monitoring focused on clinical episode frequency and, where available, molecular or biochemical correlates of response.

3.2. L-arginine and L-citrulline: Targeting vascular dysfunction

3.2.1. Vascular hypothesis and nitric oxide deficiency

Stroke-like episodes in MELAS have been linked to endothelial dysfunction and impaired nitric oxide (NO) bioavailability in cerebral microvasculature (*25*). Reported abnormalities include reduced flow-mediated dilation and elevated endothelin-1, consistent with systemic endothelial dysfunction, and mitochondrial respiratory chain impairment in vascular endothelium may reduce NO synthase activity, contributing to vasoconstriction and microcirculatory disturbance (*26*).

3.2.2. Clinical evidence for L-arginine

L-arginine, a substrate for NO synthesis, has been evaluated for both acute treatment and chronic prophylaxis in MELAS (*27*). For acute episodes, a prospective multicenter study by Koga and colleagues proposed an intravenous regimen of 0.5 g/kg L-arginine hydrochloride (maximum 30 g) administered over 30–60 minutes, ideally within 6 hours of symptom onset (*28*); in 10 patients, headache improved in 90% at 2 hours post-infusion and nausea/vomiting improved in 80%, with additional improvements in impaired consciousness and visual symptoms and no severe treatment-related adverse events reported.

For chronic prophylaxis, oral L-arginine at 150–300 mg/kg/day in 2–3 divided doses was associated with prolongation of the interictal interval during a 2-year period ($p = 0.0625$), although 7-year follow-up indicated that benefit did not fully halt progression, consistent with the progressive nature of MELAS (*28*).

A pragmatic pharmacodynamic target has been proposed: maintaining plasma arginine concentrations above 167 μmol/L, which has been associated with reduced recurrence of stroke-like episodes and can be used to guide dose optimization (*29*).

3.2.3. L-citrulline and bioavailability considerations

L-citrulline, which is converted to L-arginine *via* the arginine–citrulline cycle, may offer advantages including better oral bioavailability, reduced first-pass hepatic metabolism, and more sustained elevation of plasma arginine (*30*). A phase I dose-finding study (NCT03952234) completed in 2019 established safety and tolerability; and subsequent phase II efficacy trials are planned (*31*).

3.3. Novel small-molecule therapeutics in clinical development

Key active and recently completed interventional studies in MELAS and the broader m.3243A>G spectrum—including trials of KL1333 (FALCON), zagociguat (PRIZM), sonlicromanol (KHENERGIZE/KHENEXT transitioning to KHENERFIN), TTI 0102 (TTI MITO 001), and L citrulline—are summarized in Table 1 (*30-41*).

**Table 1. Active and recent clinical trials for MELAS and m.3243A>G spectrum disorders (2024–2026)**

| Trial Name | Intervention | Mechanism | Phase | Status | NCT Number | Primary Endpoints | Sponsor | *n* | Country/Region |
|---|---|---|---|---|---|---|---|---|---|
| Taurine Phase III | Taurine 9–12 g/day | $\tau m^5U$ modification restoration | III | Completed (approved Japan 2019) | UMIN000011908 | Complete prevention of stroke-like episodes | Tohoku Univ./ MELAS Research Group (Japan) | 31 | Japan |
| FALCON | KL1333 ($NAD^+$ modulator) | $NAD^+$:NADH ratio normalization, mitochondrial biogenesis | II | Recruiting | NCT05650229 | Fatigue severity, 6-minute walk test | Abliva AB | 180 est. | US, AU, BE, CZ, DK, FR, DE, IT, NL, ES, UK |
| PRIZM | Zagociguat 15–30 mg/day | Soluble guanylate cyclase stimulation | IIb | Active, not recruiting (43 enrolled) | NCT06402123 | Cognitive performance, fatigue | Tisento Therapeutics | 43 | US, AU, CA, DE, IT, UK |
| KHENERFIN | Sonlicromanol 100 mg BID | ROS-redox modulation | III | Recruiting (started Feb 1, 2026; est. completion Sep 30, 2028) | NCT06451757 | Physical fatigue symptoms, balance, cognition | Khondrion BV | 220 est. | US, DK, FR, DE, IT, NL, UK |
| TTI-MITO-001 | TTI-0102 (cysteamine) | Antioxidant, mitochondrial protection | II | Recruiting | NCT06644534 | Safety, efficacy, PK/PD parameters | Thiogenesis Therapeutics, Inc. | 12 est. | France, Netherlands |
| L-Citrulline Dose-Finding | L-citrulline | NO precursor, superior bioavailability | I | Completed | NCT03952234 | Safety, maximum tolerated dose | Baylor College of Medicine | 10 | United States |

*Data Sources*: ClinicalTrials.gov and EU Clinical Trials Register; all registry data accessed June 2026. *Abbreviations*: BID, twice daily; NO, nitric oxide; PK/PD, pharmacokinetics/pharmacodynamics; ROS, reactive oxygen species.

#### 3.3.1. Sonlicromanol (KH176): ROS-redox modulation

Sonlicromanol is a ROS-redox modulator; its active metabolite (KH176m/KH183) is intended to reduce oxidative stress associated with OXPHOS dysfunction (*32*) and modulate cellular redox balance. In the randomized, placebo-controlled 28-day phase IIb KHENERGIZE study in m.3243A>G MELAS spectrum disorders, the primary endpoint was not met, but multiple secondary endpoints improved (*16,33*). In the 52-week KHENEXT open-label extension, improvements were reported across cognition (Cognitive Failures Questionnaire), mood (Beck Depression Inventory), pain, fatigue, motor function (balance), and quality-of-life measures, with an acceptable safety profile and no serious adverse effects attributed to sonlicromanol (*16,34*).

These phase IIb findings supported progression to a phase III program, and the planned registrational study KHENERFIN (NCT06451757) commenced recruitment on February 1, 2026, with estimated completion September 30, 2028 (Sponsor: Khondrion BV; $n = 220$ estimated; US, Denmark, France, Germany, Italy, Netherlands, UK; ClinicalTrials.gov NCT06451757, accessed June 2026) (*42*). Sonlicromanol has also received orphan drug designation from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for several mitochondrial indications (including MELAS).

#### 3.3.2. KL1333: $NAD^+$ pathway modulation and mitochondrial biogenesis

$KL_{1333}$ is an orally bioavailable $NAD^+$ modulator that increases the $NAD^+$:NADH ratio through $NQO_1$ activation (*43*), with downstream engagement of the *SIRT1*/AMPK/$PGC_{-1\alpha}$ axis to support mitochondrial biogenesis and oxidative metabolism (*36*). In fibroblasts derived from MELAS patients harboring m.3243A>G, preclinical studies reported increased ATP production, reduced lactate and reactive oxygen species (ROS) levels, improved mitochondrial mass and membrane potential, and increased maximal oxygen consumption, alongside activation of biogenesis-related signaling (*36*).

A phase 1a/1b study evaluated safety, tolerability, and pharmacokinetics in healthy volunteers and patients with primary mitochondrial disease (*37*). The FALCON phase II study (NCT05650229) is recruiting adults with primary mitochondrial disease, including MELAS–MIDD spectrum disorders, and evaluates fatigue severity, lower-extremity function (6-minute walk test), endurance, quality of life, and biomarkers (including fibroblast growth factor 21 [FGF21] and growth differentiation factor 15 [GDF15]) over 48 weeks of treatment.

#### 3.3.3. Zagociguat: Soluble guanylate cyclase (sGC) stimulation

Zagociguat is an sGC stimulator designed to enhance

NO–cGMP signaling and address vascular dysfunction, providing a mechanistic complement to NO precursor strategies (*38*). The PRIZM phase IIb randomized, double-blind, placebo-controlled crossover trial (NCT06402123) enrolled 43 participants across the US, Australia, Canada, Germany, Italy, and UK (Sponsor: Tisento Therapeutics; ClinicalTrials.gov NCT06402123, accessed June 2026) and is evaluating 15 mg and 30 mg daily dosing versus placebo for 12 weeks in adults with genetically and phenotypically defined MELAS (*39*), with cognitive performance and fatigue severity as primary endpoints and imaging/biomarker and quality-of-life measures as secondary endpoints.

#### 3.3.4. TTI-0102: Cysteamine prodrug (antioxidant strategy)

TTI-0102 is an enteric-coated, delayed-release cysteamine formulation intended to provide mitochondrial antioxidant effects (*40*). A randomized, double-blind, placebo-controlled trial (NCT06644534; Sponsor: Thiogenesis Therapeutics, Inc.; $n$ = 12 estimated; France and Netherlands; ClinicalTrials.gov, accessed June 2026) is evaluating TTI-0102 versus placebo for up to 6 months in MELAS (*41*), using a 2:1 randomization and including an interim review after nine participants complete 3 months of treatment. Primary objectives include evaluation of efficacy, safety, and tolerability, as well as pharmacokinetics and pharmacodynamics at steady state.

A consolidated overview of major pharmacologic interventions—including taurine, L arginine/L citrulline, mitochondrial cofactors, and late stage small molecules—with their mechanisms, dosing regimens, evidence levels, principal clinical outcomes, and safety profiles is provided in Table 2 (*13,20-41,43*).

### 3.4. Gene-based therapeutic approaches: Heteroplasmy manipulation

The principal gene based therapeutic platforms under development for m.3243A>G related MELAS—including mitoTALEN/mpTALEN, mitochondria targeted zinc finger nucleases, DdCBE base editors, mitoARCUS, mitochondrial replacement therapy, and allotopic expression—are compared in Table 3 with respect to targets, mechanisms, development stage, key achievements, and remaining challenges (*18,19,44-51*).

#### 3.4.1. Mitochondria-targeted TALENs (mitoTALEN/mpTALEN)

Mitochondria-targeted transcription activator-like effector nucleases (TALENs) have been engineered by adding mitochondrial localization sequences to enable selective cleavage of mtDNA (*44*), with the goal of preferentially eliminating mutant genomes and shifting heteroplasmy toward wild type. Yahata and colleagues (2025) reported optimized mtDNA-targeted platinum TALENs (mpTALENs) enabling bidirectional heteroplasmy modification in patient-derived induced pluripotent stem cells (iPSCs) harboring m.3243A>G (*18*), including improvements intended to enhance specificity, reduce mtDNA copy-number depletion, and support controlled expression.

In that work, mpTALEN treatment yielded heteroplasmy modulation spanning approximately 11% to 97% mutant load across clones; when mutant load fell below pathogenic thresholds, differentiation capacity was restored, providing functional validation of the heteroplasmy-threshold concept (*18*). Key barriers remain, including delivery to the CNS, skeletal muscle, and heart; transient reductions in mtDNA copy number during treatment; and the possibility that repeat dosing may be needed over time.

#### 3.4.2. CRISPR-free base editing: DdCBE and related editors

Because guide RNAs do not readily traverse mitochondrial membranes, conventional CRISPR-Cas approaches are not directly applicable in mitochondria (*19*); DdCBE (DddA-derived cytosine base editor) addresses this limitation using TALE DNA-binding domains fused to split halves of a deaminase to enable mtDNA base editing without guide RNAs or double-strand breaks. Recent work has focused on improving specificity and product purity, demonstrating correction of pathogenic variants in patient-derived systems, and refining delivery modalities (including mRNA-based approaches (*45*) and lipid nanoparticle formulations) to move toward clinical translation (*46*).

For m.3243A>G specifically, direct sequence correction requires A→G (adenine-to-guanine) base editing, which is not achievable with current DdCBE platforms that only enable C→T conversions; this represents a fundamental limitation for direct m.3243A>G correction. The ongoing development of mitochondrial adenine base editors (mitoABEs) is the critical enabling step (*52*), though published mitoABE tools remain at proof-of-concept stages and have not yet been applied to the *MT-TL1* locus in patient-derived cells.

#### 3.4.3. Engineered meganucleases: mitoARCUS

mitoARCUS is an engineered meganuclease platform tailored for mitochondrial applications; preclinical work has demonstrated elimination of mutant mtDNA (including m.3243G) with resultant heteroplasmy shifts and functional improvements in cellular respiration consistent with the heteroplasmy reduction achieved (*53*). Current development efforts focus on optimizing delivery strategies and tissue targeting for *in vivo* use. Critically, all published mitoARCUS work for MELAS remains at

**Table 2. Pharmacological interventions for m.3243A>G MELAS: mechanisms and evidence Levels**

| Intervention | Mechanism of Action | Dosing Regimen | Evidence Level | Key Clinical Results | Safety Profile |
|---|---|---|---|---|---|
| Taurine | Restoration of τm$^5$U modification in mt-tRNA^Leu(UUR)^ | 9–12 g/day PO divided TID | Level I | 60% complete stroke-like episode prevention; 80% ≥50% reduction | Well-tolerated; no severe AEs; 9+ years safety data |
| L-Arginine IV | Acute NO precursor, vasodilation | 0.5 g/kg (max 30 g) IV over 30–60 min during episodes | Level II | 90% headache improvement; 80% nausea/vomiting improvement | Safe for acute use |
| L-Arginine PO | Chronic NO precursor, prophylaxis | 150–300 mg/kg/day PO divided BID–TID | Level II | Extended interictal phase; target plasma level >167 μmol/L | Well-tolerated long-term |
| L-Citrulline | NO precursor, superior bioavailability | Under investigation | Level III | Dose-finding complete; phase II planned | Phase I: acceptable safety |
| Sonlicromanol | ROS-redox modulation, antioxidant | 100 mg PO BID | Level III | Improved cognition (CFQ), mood (BDI), pain, fatigue, balance | No serious AEs; well-tolerated |
| KL1333 | $NAD^+$ pathway enhancement, *SIRT1/PGC-1α*/AMPK/*PGC-1α* activation | Under investigation | Level II | Preclinical: ↑ATP, ↓lactate, ↑mitochondrial mass in MELAS cells | Phase I: well-tolerated |
| Zagociguat | Soluble guanylate cyclase stimulation, NO-cGMP pathway | 15–30 mg/day PO | Level II | Ongoing (PRIZM trial recruiting) | Under evaluation |
| TTI-0102 | Cysteamine prodrug, antioxidant | Under investigation | Level II | Ongoing (TTI-MITO-001 recruiting) | Under evaluation |
| CoQ10/Ubiquinol | Electron transport chain cofactor, antioxidant | 300–600 mg/day PO | Level III | Variable individual responses; part of standard cocktail | Well-tolerated |
| *Idebenone* | *Synthetic CoQ10 analog, enhanced mitochondrial penetration* | *900–2,250 mg/day PO* | *Level II* | *Reduced cerebral lactate in small studies; inconsistent results* | *Generally well-tolerated* |

*Evidence Level criteria*: Level I, peer-reviewed RCT or meta-analysis; Level II, open-label trial or comparative cohort; Level III, single-arm study, registry data, or company-reported data; Level IV, case series, preclinical study, or expert consensus. *Abbreviations*: AE, adverse event; BDI, Beck Depression Inventory; BID, twice daily; CFQ, Cognitive Failures Questionnaire; CoQ10, coenzyme Q10; IV, intravenous; NO, nitric oxide; PO, per os (oral); TID, three times daily; τm$^5$U, 5-taurinomethyluridine.

**Table 3. Gene-based therapeutic approaches for m.3243A>G MELAS: technology platforms and translational status**

| Technology | Platform | Target | Mechanism | Development Stage | Key Achievements | Major Challenges |
|---|---|---|---|---|---|---|
| mitoTALEN/ mpTALEN | Mitochondria-targeted TALENs | Mutant mtDNA elimination | Selective cleavage of mutant genomes → heteroplasmy shift | Preclinical | Heteroplasmy modulation 11%–97% in m.3243A>G-iPSCs; restoration of differentiation capacity | Tissue delivery (CNS, muscle); mtDNA copy number management; repeated dosing requirements |
| mtZFN | Mitochondria-targeted zinc finger nucleases | Mutant mtDNA elimination | Obligate heterodimeric nucleases cleave mutant mtDNA | Preclinical | Heteroplasmy reduction in cybrids; restored respiration | Optimization of specificity; delivery systems |
| DdCBE | DddA-derived cytosine base editor | Point mutation correction (C→T editing) | Split deaminase + TALE binding → precise base editing without DSBs | Preclinical | Functional correction of m.4291T>C in patient cells; high specificity for target editing | Development of ABEs for A→G correction needed for m.3243A>G; off-target nuclear editing risk |
| mitoARCUS | Engineered meganuclease | m.3243G elimination | Designed nuclease with high specificity for m.3243G | Preclinical | Efficient heteroplasmy shift in patient cells; functional improvement | Delivery optimization; *in vivo* validation |
| MRT | Mitochondrial replacement therapy | Prevention of transmission | Nuclear transfer to enucleated donor oocyte | Clinical (reproductive) | 8 babies born (UK, July 2025); prevention of high-level mutation transmission | Carryover mtDNA (0.5%–2%); reversion risk; not applicable to affected patients |
| Allotopic expression | Nuclear gene relocation | Protein replacement | MT-encoded genes relocated to nucleus; protein imported to mitochondria | Phase III (LHON only) | FDA/EMA approval for *ND4* (LUMEVOQ) in LHON | Not applicable to tRNA genes (*MT-TL1*); import mechanisms differ |

*Abbreviations*: ABE, adenine base editor; CNS, central nervous system; DdCBE, DddA-derived cytosine base editor; DSB, double-strand break; iPSC, induced pluripotent stem cell; LHON, Leber hereditary optic neuropathy; MRT, mitochondrial replacement therapy; mtDNA, mitochondrial DNA; mtZFN, mitochondria-targeted zinc finger nuclease; TALEN, transcription activator-like effector nuclease.

the preclinical stage; no human therapeutic application has been reported. Key barriers to clinical translation include efficient delivery to post-mitotic tissues (CNS, skeletal muscle, and cardiac muscle), long-term stability of heteroplasmy shifts, and regulatory pathways for mitochondria-targeted nucleases.

## 4. Discussion

### 4.1. Paradigm shift from symptomatic to disease-modifying therapy

Over the past decade, mechanistic insight into m.3243A>G pathophysiology has fundamentally reshaped the therapeutic landscape for MELAS (*5,13,24*). The regulatory approval of high-dose taurine supplementation in Japan represents a milestone: it is the first disease-modifying therapy that targets an underlying molecular defect (taurine modification deficiency) rather than focusing solely on symptomatic management (*14,20,23,24*).

The phase III findings—showing complete prevention of stroke-like episodes in 60% of treated participants—set a new benchmark for clinically meaningful benefit in this population (*23*). Importantly, measurement of $\tau m^5U$ modification rates provides pharmacologic proof of target engagement and supports biological plausibility that correcting the molecular defect can translate into clinical benefit (*21,23*). Available long-term observations (including treatment beyond 9 years in some patients) further support the feasibility of sustained administration without clear evidence of cumulative toxicity, although rigorous long-term comparative data remain limited, underscoring the need for post-marketing surveillance studies (*22*).

At the same time, taurine is not a panacea for the multisystem burden of MELAS. The disease reflects convergent dysfunction across mitochondrial translation, bioenergetics, redox homeostasis, vascular signaling, and compensatory pathways such as mitochondrial biogenesis. This complexity provides a strong rationale for mechanism-based add-on therapies that address complementary nodes of pathophysiology, particularly for patients with persistent neurologic events, progressive myopathy, or significant systemic involvement despite optimized foundational care (*5,15,32,36*).

### 4.2. Multi-hit therapeutic model: Rationale for combination approaches

The pathophysiology of MELAS encompasses multiple interacting mechanisms, including mt-tRNA modification defects, respiratory chain dysfunction, oxidative stress, nitric oxide (NO) deficiency with endothelial dysfunction, and impaired mitochondrial biogenesis. This pathophysiology supports a proposed conceptual multi-hit therapeutic strategy in which therapies are layered to target distinct mechanisms rather than relying on a single agent to address all clinically relevant pathways (*5,15,32,43,54*).

In my proposed tiered framework, the "current standard" layer includes evidence-based pharmacotherapy such as taurine to address the taurine modification defect (*14,20,23*), NO precursor strategies (L-arginine and/or L-citrulline) to mitigate vascular dysfunction (*25-29*), and selected cofactors commonly used in mitochondrial practice (*e.g.*, coenzyme Q10, riboflavin, and L-carnitine) as supportive measures (*13*). Beyond this foundation, late-stage investigational agents provide plausible complementary benefits: sonlicromanol may mitigate redox imbalance and improve patient-centered outcomes (*e.g.*, fatigue and mood) (*32-35*), while KL1333 may enhance mitochondrial biogenesis and energy metabolism by modulating $NAD^+$ pathways (*36,37,43*); zagociguat may augment NO–cGMP signaling through soluble guanylate cyclase stimulation, potentially complementing NO precursor therapy (*38,39*).

This tiered approach is intended to be practical: it mirrors how clinicians often escalate therapy when a patient's phenotype remains active despite baseline measures, while still grounding escalation in mechanistic plausibility and emerging trial evidence (*32,37,39,43*).

Combination strategies also reflect the clinical heterogeneity of MELAS. Stroke-like episodes may dominate in one patient, whereas myopathy, neuropsychiatric symptoms, cardiomyopathy, or endocrine manifestations may dominate in another. In this context, a flexible multi-hit model can serve as a clinical reasoning scaffold: it helps align therapy selection with the most salient pathophysiologic drivers and measurable outcomes for an individual patient rather than applying a "one-size-fits-all" regimen (*6,7,9,11,54*).

This tiered, mechanism-based approach is integrated into a proposed conceptual multi-hit therapeutic framework (presented here as a conceptual guide for clinicians, not a validated clinical algorithm), incorporating lifestyle measures, evidence-based pharmacotherapy, advanced small molecules, and emerging gene-based strategies.

### 4.3. Challenges in clinical trial design for MELAS

Several intrinsic features of MELAS complicate conventional trial design. First, disease heterogeneity is substantial: age at onset, organ involvement, clinical severity, and event frequency vary widely, and heteroplasmy levels differ across tissues and change over time (*6,55*). Second, patient numbers are limited by rarity and geographic dispersion, necessitating multicenter collaboration and careful enrollment criteria to preserve internal validity without making recruitment infeasible (*37,39*). Third, endpoint selection is difficult: stroke-like episodes are episodic and unpredictable, and short-duration studies may miss clinically meaningful changes

in a progressive disease with variable trajectories (*23,37,39*).

To address these constraints, current trials increasingly incorporate patient-reported outcomes, multidomain functional measures, and biomarker panels designed to capture signal across heterogeneous phenotypes (*37,39*). Adaptive and crossover designs can improve efficiency when sample sizes are small, although they introduce analytic complexity and require careful attention to carryover effects and event timing 38,40. The ongoing phase II programs discussed in this review illustrate this trend by pairing clinical outcomes (fatigue, cognition, function, quality of life) with biomarkers (*e.g.*, FGF21, GDF15) and imaging (*e.g.*, MRI/magnetic resonance spectroscopy [MRS]) to triangulate efficacy (*37,39,56*).

Another persistent limitation is the absence of head-to-head comparisons among foundational therapies (*e.g.*, taurine *vs.* L-arginine *vs.* combination regimens) and among investigational agents. Without comparative effectiveness data, treatment choices often rely on a synthesis of mechanistic rationale, limited clinical datasets, tolerability considerations, and patient-specific phenotype rather than definitive superiority evidence (*13,23,32,38,43*).

### 4.4. Precision medicine framework: Genotype-guided therapy selection

A precision medicine approach to MELAS requires integrating genotype, phenotype, and biomarkers to guide therapy selection and monitoring. Mutation-specific biology matters: taurine therapy is mechanistically aligned with the taurine modification defect associated with m.3243A>G and some related *MT-TL1* variants, whereas other mitochondrial genotypes may require different targeting strategies (*14,20,23*). Phenotype-based stratification is equally important. For example, a patient with frequent stroke-like episodes may warrant aggressive optimization of taurine plus NO pathway support, whereas a patient with prominent myopathy and fatigue may be a better candidate for therapies targeting mitochondrial biogenesis or redox balance as those agents mature in clinical development (*5,57*).

Biomarkers can support both baseline stratification and longitudinal monitoring, but their roles remain imperfect. FGF21 and GDF15 are among the most studied circulating biomarkers for mitochondrial disease burden and may correlate with severity (*56*); plasma arginine monitoring can guide NO precursor dosing and offers a practical pharmacodynamic target (*29*); $\tau m^5U$ modification rate (where available) offers a uniquely direct measure of taurine target engagement (*21,23*). Serial heteroplasmy measurements can add context, but interpretation must account for tissue specificity and age-related dynamics, particularly the decline of blood heteroplasmy over time (*58*).

In practice, the goal is to move from empiric escalation to data-informed adjustment—selecting therapies based on a patient's most actionable pathophysiologic drivers and using feasible clinical and biomarker endpoints to evaluate benefit. Achieving this will require prospective validation linking biomarker shifts to clinically meaningful outcomes, especially across diverse ages and phenotypes (*37,39,56,57*).

A structured summary of candidate genetic, biochemical, imaging, and functional biomarkers—including blood and urine heteroplasmy, FGF21, GDF15, plasma L arginine, lactate, $\tau m^5U$ modification rate, brain MRS metrics, and exercise capacity measures—is presented in Table 4 to guide disease monitoring and assessment of treatment response (*21,23,29,37,39,52,56-58*).

### 4.5. Gene therapy: Transformative potential and remaining hurdles

Gene-based strategies offer the most direct route to addressing the root genetic defect by shifting heteroplasmy or editing pathogenic mtDNA. Proof-of-concept studies using mitochondria-targeted nucleases (including optimized TALEN-based approaches) demonstrate that heteroplasmy can be modulated in patient-derived systems and that reducing mutant load below pathogenic thresholds can restore cellular phenotypes, supporting the therapeutic premise (*18,19,44*).

However, formidable translational barriers remain. Effective delivery to clinically relevant tissues—particularly the central nervous system, skeletal muscle, and heart—is a primary challenge, and delivery platforms must balance efficiency with safety (*44,51,53*). Additional concerns include transient reductions in mtDNA copy number during nuclease activity, durability of heteroplasmy shifts over time in dividing tissues (*18,44,59*), and the need for rigorous evaluation of off-target effects and long-term genotoxicity (*59*). Regulatory pathways for mtDNA therapies must also contend with unique issues such as tissue-specific heteroplasmy thresholds and the complexity of defining validated surrogate endpoints (*24,60*).

Despite these constraints, progress from 2020 to 2026 has been rapid, and the direction of the field suggests that early human trials may become feasible within the next decade if delivery and safety hurdles can be addressed. For clinicians and investigators, these advances reinforce the importance of developing standardized outcome measures, biomarkers, and natural history datasets now, so that emerging genetic therapies can be evaluated efficiently and responsibly when they reach clinical testing (*51,59,60*).

## 5. Conclusions

The therapeutic landscape for m.3243A>G-associated

**Table 4. Biomarkers for disease monitoring and treatment response assessment in MELAS**

| Biomarker Category | Specific Markers | Clinical Utility | Advantages | Limitations | Target Range/Interpretation | Validation Status/Clinical Applicability |
|---|---|---|---|---|---|---|
| Genetic | Blood heteroplasmy (m.3243A>G %) | Diagnosis, genotype confirmation | Noninvasive, widely available | Age-dependent decline; tissue discordance | Diagnostic threshold >10%–20%; severity correlation imperfect | Routine clinical use; Diagnosis (D), Monitoring (M) |
| Genetic | Urine epithelial cell heteroplasmy | Better phenotype correlation *vs.* blood | Noninvasive, more stable than blood | Intrapatient variability; requires specialized testing | Generally higher than blood; better reflects disease burden | Specialist centre; Diagnosis (D), Monitoring (M) |
| Biochemical | FGF21 (serum) | Disease severity, treatment response | Strong diagnostic accuracy (AUC 0.81); correlates with myopathy | Elevated in other mitochondrial/ muscle disorders; limited CNS specificity | Elevated in MELAS; decreasing levels may indicate treatment response | Specialist centre; Monitoring (M), Treatment response (T) |
| Biochemical | GDF15 (serum) | Disease severity, multisystem involvement | Highest diagnostic accuracy (AUC 0.89); correlates with IPMDS score | Nonspecific (elevated in inflammation, malignancy) | Elevated in MELAS; serial measurements track disease burden | Specialist centre; Monitoring (M), Prognosis (P) |
| Biochemical | Plasma L-arginine | Guide L-arginine/L-citrulline dosing | Direct pharmacodynamic marker for NO pathway therapy | Acute fluctuations with meals, stress | Target >167 μmol/L for stroke-like episode prevention | Specialist centre; Monitoring (M), Treatment response (T) |
| Biochemical | Plasma/CSF lactate | Metabolic derangement | Widely available, real-time metabolic status | Variable with exercise, feeding; may be normal between episodes | Elevated during acute episodes; lactate:pyruvate ratio >20 suggestive | Routine clinical use; Monitoring (M) |
| Biochemical | $\tau m^5U$ modification rate | Taurine therapy efficacy | Direct mechanistic biomarker; validates molecular correction | Specialized research assay; limited availability | Increased with taurine treatment; correlates with clinical benefit | Research setting only; Treatment response (T) |
| Imaging | Brain MRS (lactate peak) | Active stroke-like lesion | Noninvasive localization of metabolic dysfunction | Requires specialized MRI protocol and expertise | Elevated lactate peak at 1.3 ppm in active lesions | Specialist centre; Diagnosis (D), Monitoring (M) |
| Imaging | Brain MRS (NAA) | Neuronal integrity | Marker of neuronal loss/ dysfunction | Nonspecific for mitochondrial disease | Reduced NAA in affected regions; marker of irreversible damage | Specialist centre; Monitoring (M), Prognosis (P) |
| Functional | 6-minute walk test | Exercise capacity, functional status | Standardized, reproducible, clinical trial endpoint | Affected by comorbidities (cardiac, pulmonary, orthopedic) | Baseline varies; improvement ≥ 30 m considered clinically meaningful | Routine clinical use; Monitoring (M), Treatment response (T) |
| Functional | $VO_2$max, anaerobic threshold | Whole-body mitochondrial capacity | Objective measure of OXPHOS function | Requires specialized equipment and protocols | Reduced in MELAS; improvement indicates enhanced mitochondrial function | Specialist centre; Monitoring (M), Treatment response (T) |

*Abbreviations*: AUC, area under the curve; CNS, central nervous system; CSF, cerebrospinal fluid; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; IPMDS, International Paediatric Mitochondrial Disease Scale; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; NO, nitric oxide; OXPHOS, oxidative phosphorylation; $\tau m^5U$, 5-taurinomethyluridine; $VO_2$max, maximal oxygen consumption.

MELAS has changed substantially over the past decade (*5,13,24*). The regulatory approval of high-dose taurine supplementation—showing complete prevention of stroke-like episodes in 60% of participants in a phase III study and demonstrating mechanism-based correction of the taurine modification defect—marks a decisive shift from purely symptomatic management toward disease-modifying therapy (*20,23*).

Multiple late-stage and emerging therapies are now expanding the mechanistic scope of intervention. Ongoing trials of novel small molecules—including sonlicromanol (a ROS-redox modulator advancing to phase III development) (*32-35*), KL1333 (an $NAD^+$ pathway modulator in phase II evaluation) (*36,37,43*), zagociguat (an sGC stimulator in phase IIb) (*38,39*), and TTI-0102 (a cysteamine prodrug in phase II)—offer complementary approaches that target oxidative stress, mitochondrial biogenesis, and vascular signaling (*40,41*). The convergence of these programs supports a multi-hit treatment paradigm in which therapies are selected and layered to address the dominant pathophysiologic drivers in an individual patient (*40,54*).

Gene-based strategies may ultimately be the most transformative by directly addressing the genetic basis of disease through heteroplasmy manipulation. Mitochondria-targeted nucleases (including mitoTALEN/mpTALEN) (*18,44*), CRISPR-independent base editing platforms (*e.g.*, DdCBE and related editors) (*19,45,46,52*), and engineered meganucleases (mitoARCUS) have demonstrated proof of concept in patient-derived systems, including meaningful heteroplasmy shifts with restoration of mitochondrial function (*18,53*). Major translational challenges remain—particularly safe and efficient delivery to the central nervous system and muscle and the need for rigorous long-term safety data (*51,59*)—but progress from 2020 to 2026 suggests a realistic pathway toward first-in-human studies within the next decade (*60*).

Looking ahead, I expect the greatest clinical gains to come from precision medicine strategies (*57*) that integrate genotype, phenotype, and biomarkers to guide therapy selection and monitoring (*37,39,56*). As additional disease-modifying therapies mature, patients and families affected by MELAS have reason for cautious optimism that the historically progressive course of this disorder may become increasingly modifiable through targeted, mechanism-based interventions (*32,43,44*).

This narrative review has several limitations. The evidence base for most therapeutic agents discussed remains early-stage: most small-molecule trials involve fewer than 50 participants, and many are open-label in design. Data for sonlicromanol's phase IIb outcomes include company-reported results (*33,34*) in addition to the peer-reviewed publication (*16*); TTI-0102 results (*41*) derive from a clinical trial registry entry for a 12-participant study. Several gene-based strategies (mitoTALEN, DdCBE, mitoARCUS) remain at preclinical stages with no human therapeutic application reported to date. The multi-hit therapeutic model presented here is a proposed conceptual framework and has not been prospectively validated in clinical trials. Most clinical evidence derives from adult populations in Japan, Europe, and North America, limiting generalizability. Biomarker thresholds and treatment-response criteria require prospective validation. As a narrative synthesis, this review may be subject to selection bias, and comprehensiveness is not guaranteed.

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