PRERELEASE – UNDER EMBARGO

Khondrion announces publication of qualitative study informing endpoint selection for the KHENERFIN phase 3 trial in m.3243A>G primary mitochondrial disease

Study reports patient-derived content-validity findings for physical and mental fatigue measures and describes related impacts on daily functioning.

NIJMEGEN, the Netherlands — 1 September 2026 — Khondrion B.V. today announced the publication of a qualitative study in *Orphanet Journal of Rare Diseases* examining the lived experience of adults with genetically confirmed m.3243A>G primary mitochondrial disease (PMD).

Smeitink, J., Hoogstraten, C.A., Janssen, M.C. et al. **A qualitative study assessing content validity of Neuro-QoL fatigue and PROMIS mental fatigue in m.3243A>G primary mitochondrial disease.** *Orphanet J Rare Dis (2026)*. https://doi.org/10.1186/s13023-026-04573-2

The publication provides patient-derived evidence on the content validity and suitability of two fatigue measures, which informed selected elements of Khondrion's KHENERFIN endpoint strategy. KHENERFIN (NCT06451757) is Khondrion's pivotal, randomized, placebo-controlled Phase 3 study of sonlicromanol, an investigational new drug. KHENERFIN is specifically designed to evaluate efficacy and safety in adults with genetically confirmed m.3243A>G PMD.

m.3243A>G PMD is a progressive genetic disorder that affects multiple organ systems, especially those most energy demanding. It produces a range of symptoms, including physical and mental fatigue, muscle weakness, hearing loss, and pain. While no single clinical measure can fully capture how these symptoms shape a patient's daily life, physical fatigue and lower-limb weakness are among the symptoms most frequently reported — and experienced as most burdensome — by adults with m.3243A>G PMD. KHENERFIN's endpoint strategy was

purpose-built around these patient-reported experiences, focusing on two domains central to daily functioning: physical fatigue and lower-limb function, including muscle strength and balance.

What the publication contributes

- **For clinical communication:** The study provides structured terminology for symptoms, including mental fatigue, that participants described as difficult to communicate. This may support clearer discussion of symptoms with clinicians and others.
- **For the KHENERFIN endpoint strategy:** The study provides patient-derived content-validity evidence supporting the relevance and comprehensibility of selected fatigue concepts considered in the clinical trial.
- **For future research:** The findings inform the evaluation of physical and mental fatigue and related physical-function concepts in future clinical studies.

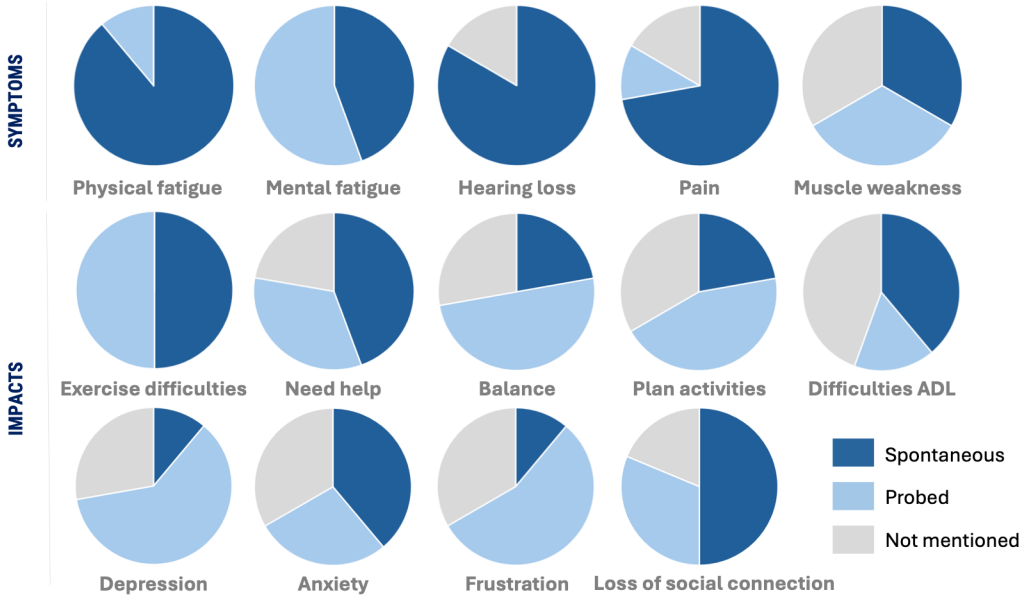
Key findings

The publication describes the results of concept elicitation interviews with adults living with genetically confirmed m.3243A>G PMD, who described how the disease affects their daily lives, followed by cognitive debriefing interviews assessing whether two fatigue measures — the Neuro-QoL Short Form v1–Fatigue and the newly developed PROMIS Mental Fatigue–Mitochondrial Disease Short Form — reflected those experiences.

- The study included adults with genetically confirmed m.3243A>G PMD recruited in the United States and the Netherlands.
- In 18 concept elicitation interviews, participants described 21 disease-related signs and symptoms. Physical fatigue, mental fatigue, hearing loss, and pain were among the most frequently reported and bothersome.
- Participants described impacts on exercise and physical functioning, activities of daily living, emotional well-being, social participation, and work or school.
- The Neuro-QoL Short Form v1–Fatigue captured the core physical fatigue concepts identified by participants and was generally considered understandable, relevant, and suitable for a seven-day recall period.
- The identified mental fatigue concepts informed development of an eight-item PROMIS Mental Fatigue–Mitochondrial Disease Short Form, which participants also considered understandable and relevant.
- Most participants considered a one-category change on an item to be meaningful in their daily lives. The latter was a qualitative, hypothetical assessment and should not be interpreted as an established responder's threshold.

RESULTS

SYMPTOMS AND IMPACTS THAT AFFECT QUALITY OF LIFE



PROMIS MF-MD SF CAPTURES MD PATIENT EXPERIENCES OF MENTAL FATIGUE

CE concept	Physically exhausted	No energy	Broad fatigue	ADL difficulties	Home-bound	Frustration	Physically tired	Left out socially	**Mental fatigue**
Neuro-QoL SFv1-F item	1 Exhausted	2 No energy	3 Fatigued	4 Tired for chores	5 Tired to go out	6 Frustrated being tired	7 Tired	8 Limit social activity	**Not captured**
Understanding	100%	100%	100%	100%	100%	100%	100%	100%	
Relevance	100%	100%	100%	100%	94.4%	100%	100%	100%	

CE concept	Thinking difficulty	Memory difficulty	Trouble finish tasks	Organizing thoughts	Trouble start tasks	Holding conversations	Tired to think clearly	No energy mentally
PROMIS MF-MD SF	1 Slowed down in thinking	2 More forgetful	3 Trouble finish tasks	4 Organizing thoughts	5 Trouble start tasks	6 Efforts holding conversations	7 Tired to think clearly	8 Totally drained
Understanding	100%	100%	100%	100%	100%	100%	94.1%	100%
Relevance	94.1%	100%	100%	100%	100%	94.1%	100%	100%

What this publication informs

The study informs selected KHENERFIN endpoints and their interpretation by:

- supporting the relevance of physical fatigue as a reported patient experience in adults with m.3243A>G PMD;
- providing patient-relevant evidence concerning physical functioning and functional impacts in daily activities, including balance and mobility-related experiences; and
- informing the evaluation of mental fatigue concepts in future clinical research.

Jasper Levink, Chief Executive Officer, Khondrion B.V. - “Patients are at the center of Khondrion. This publication shows how that principle translates into clinical development: we listen to people living with mitochondrial disease, identify the functions and symptoms that matter in daily life, and use that evidence to shape our pivotal programme. The study supports the focus of KHENERFIN on physical fatigue and lower-limb function, while the additional assessment of mental fatigue will help us interpret results in the context of a genuinely multisystem disease.

We want to thank the patients and investigators who made this study possible — their willingness to share their experience is what allows us to build a pivotal programme that truly reflects patients' needs.”

About KHENERFIN

KHENERFIN is a pivotal, randomized, placebo-controlled Phase 3 study evaluating the efficacy and safety of sonlicromanol in adults with genetically confirmed m.3243A>G primary mitochondrial disease. The 52-week study will assess predefined efficacy and safety endpoints relating to patient-reported physical fatigue and lower-limb function, with mental fatigue evaluated as an additional patient-reported dimension. For more information about KHENERFIN, visit ClinicalTrials.gov (NCT06451757).

KHENERFIN's endpoint strategy was informed by two complementary sources of evidence: patient-reported priorities and findings from Khondrion's published Phase 2b programme.

The Phase 2b programme included a 28-day randomized, placebo-controlled, three-period crossover study in 27 adults with m.3243A>G-associated primary mitochondrial disease, followed by a 52-week open-label extension. The prespecified randomized-study primary endpoint—attention measured by the Cogstate visual identification task—did not demonstrate a statistically significant treatment effect in the primary analysis. Post hoc baseline-severity-adjusted analyses and analyses of secondary outcomes generated exploratory findings across selected cognitive, mood and patient-reported domains; these analyses were not adjusted for multiplicity.

The open-label extension included 15 participants, with 12 included in the extension analysis set. The publication reported changes from baseline in several exploratory measures, including fatigue, physical health, pain and balance. Because the extension was open-label, included a small number of participants and evaluated multiple outcomes without a placebo comparator, these observations cannot be attributed reliably to sonlicromanol treatment. The publication also reports limited safety and tolerability observations, which should not be interpreted as characterizing the product's safety profile.

The Phase 2b programme did not establish the efficacy or disease-modifying effect of sonlicromanol. Its findings informed further evaluation and selected elements of the KHENERFIN endpoint strategy. Together with the patient-derived content-validity evidence described in this release, the Phase 2b findings informed the selection and evaluation of endpoints for KHENERFIN.

The m.3243A>G PMD spectrum includes different clinical presentations, including classic MELAS, maternally inherited diabetes and deafness (MIDD), chronic progressive external ophthalmoplegia and mixed phenotypes. Classic MELAS is therefore one presentation within the broader m.3243A>G PMD spectrum and is not synonymous with the full study population.

Ref: Smeitink J, et al. **Phase 2b program with sonlicromanol in patients with mitochondrial disease due to m.3243A>G mutation.** *Brain*. 2025;148:896–907. doi:10.1093/brain/awae277.

About the study

The study used concept elicitation interviews to explore participants' lived experience of symptoms and impacts, followed by cognitive debriefing interviews to assess the relevance, comprehensibility, and suitability of the Neuro-QoL Short Form v1–Fatigue and the draft PROMIS Mental Fatigue–Mitochondrial Disease Short Form. The study corroborates and extends the patient priorities identified in UMDF's Voice of the Patient report, translating those broader patient priorities into content-validity evidence specific to the m.3243A>G variant.

The study included adults with genetically confirmed m.3243A>G PMD. Concept elicitation interviews included 18 participants, and cognitive debriefing interviews included 17. Participants were recruited in the United States and the Netherlands.

This was a non-interventional qualitative study. It did not evaluate the efficacy or safety of sonlicromanol or any other treatment. The study provides content-validity evidence and patient-relevance evidence for endpoint selection; it does not establish psychometric validation, responsiveness, a confirmed clinically meaningful change threshold, treatment efficacy, or disease modification. It also does not establish the magnitude or durability of a treatment effect, validate the full pivotal endpoint package, resolve statistical or multiplicity considerations, or remove risks related to recruitment, missing data, trial execution, regulatory review, or reimbursement — those questions can only be addressed by the KHENERFIN randomized, placebo-controlled study and the totality of evidence.

This study reflects a collaboration between Khondrion's clinical and patient-engagement team, clinical experts at Radboud University Medical Center (Nijmegen, the Netherlands) and Massachusetts General Hospital and Harvard Medical School (Boston, USA), and Clinical Outcomes Solutions, a specialist outcomes-research consultancy with offices in the UK and the United States that led the concept elicitation and cognitive debriefing interviews, and contributed expertise in content-validity methodology.

This study was funded by Khondrion B.V. Several authors are Khondrion employees. Clinical Outcomes Solutions employees contributed to the study design, interviews, analysis and/or interpretation, as described in the publication. Full author affiliations, contributions and competing-interest disclosures are available in the published article.

Study limitations

The study was qualitative and included a small sample recruited from two countries. All participants identified as White or Northern/Western European, and the findings may not generalize to people with other genetic causes of primary mitochondrial disease or to all populations with m.3243A>G-associated disease. The draft mental fatigue measure requires further quantitative evaluation, including assessment of its psychometric properties and ability to detect meaningful change. The study did not evaluate or validate the specific lower-limb performance measure used in KHENERFIN.

About Khondrion B.V.

Khondrion B.V. is a privately held, clinical-stage biotechnology company based in Nijmegen, the Netherlands. Patients are central to the company's mission. Khondrion is investigating therapies intended to address biological mechanisms that may contribute to mitochondrial disease progression.

Khondrion's lead programme is sonlicromanol, an oral, brain-penetrant redox and ferroptosis-modulating small molecule in late-stage clinical development for genetically defined primary mitochondrial disease caused by the m.3243A>G mitochondrial DNA variant. Sonlicromanol is being investigated for its potential effects on downstream consequences of mitochondrial dysfunction; it is not approved for commercial use.

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