Khondrion announces publication in *Brain* of integrated Phase 2b program demonstrating disease-modifying potential of sonlicromanol in primary mitochondrial disease

NIJMEGEN, the Netherlands – 7 November 2024: Khondrion, a clinical stage biopharmaceutical company discovering and developing therapies targeting primary mitochondrial disease (PMD), today announced the publication of results from its integrated Phase 2b clinical development program of sonlicromanol in the peer-reviewed scientific journal, *Brain*.

Sonlicromanol, Khondrion's lead proprietary drug candidate, is a disease-modifying, potentially first-in-class, brain-penetrant redox-modulator with anti-inflammatory properties, that targets key metabolic and inflammatory pathways underlying PMD.

The Phase 2b program in adults with the most common genetic defect causing PMD, m.3243A>G, consisted of a 28-day, randomized, placebo-controlled, three-way cross-over, dose-finding study (27 patients), complemented by a 52-week, open-label extension study. Selected outcome measures based on the most burdensome symptoms experienced by patients, including muscle weakness, chronic fatiugue, pain and cognitive decline, were studied throughout the program.

The paper's researchers highlight strong patient benefits from sonlicromanol in multiple outcome measures of global health, quality of life, mood, fatigue, pain and balance control. In patients experiencing more severe symptoms at baseline, treatment effects from sonlicromanol were more pronounced, and longer-term treatment brought continuously improving patient benefits. Given that improvements were demonstrated in multiple domains frequently affected by PMD, such as the brain and muscle, treatment effects were established to be systemic. In line with previous completed clinical trials for sonlicromanol, the drug candidate showed excellent pharmacokinetics and a positive safety profile, well tolerated through 52 weeks.

Prof. Dr. Jan Smeitink, Chief Executive Officer at Khondrion, said: *"The clinical significance of this comprehensive data set is considerable, providing strong evidence of the positive impact that sonlicromanol can offer to patients with primary mitochondrial disease, who currently have no treatment options available to them. To our knowledge, this is the first time a trial has shown clear reversal of the hallmark phenotypical symptoms in otherwise progressive mitochondrial disease."*

"In undertaking this trial we were mindful of, but not daunted by, the challenges mitochondrial diseases present to clinical development. Beyond growing substantially our understanding of the long-term safety and efficacy potential of sonlicromanol, we are pleased that through this Phase 2b program we have made fundamental progress in further validating outcome measures that will support follow-up clinical research towards market authorization. Our sincere thanks to the patients and their families, the clinical study teams and the patient advocacy community, for their contributions to this program."

Learnings from the Phase 2b program, alongside data from Khondrion's two earlier short-term safety and signal-seeking studies, have provided comprehensive insights to optimize the design – including the selection of primary and other endpoints – of the company's planned pivotal 52-week Phase 3 study, which will further investigate the potential of sonlicromanol in adult m.3243A>G patients.

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Reference

Phase 2b program with sonlicromanol in patients with mitochondrial disease due to m.3243A>G mutation. Jan Smeitink, Just van Es, Brigitte Bosman, Mirian CH Janssen, Thomas Klopstock, Grainne Gorman, John Vissing, Gerrit Ruiterkamp, Chris J. Edgar, Evertine J Abbink, Rob van Maanen, Oksana Pogoryelova, Claudia Stendel, Almut Bischoff, Ivan Karin, Mahtab Munshi, Anne Kümmel, Lydia Burgert, Christianne Verhaak, Herma Renkema https://doi.org/10.1093/brain/awae277.

Notes to editors

About Khondrion

Khondrion is a clinical stage biopharmaceutical company developing therapies for patients with primary mitochondrial disease (PMD). The company's lead asset, sonlicromanol, is a potentially first-in-class, brain-penetrant redox-modulator with anti-inflammatory properties, that targets key metabolic and inflammatory pathways underlying PMD.

One of the most advanced, disease-modifying drug candidates for mitochondrial disease in development, sonlicromanol has been tested in four clinical trials in patients with m.3243A>G PMD, as well as in the first wave of a 6-month Phase 2 study in children with genetically confirmed PMD and who suffer from motor symptoms.

Sonlicromanol has been granted orphan drug designations for the treatment of MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), Leigh disease and patients with maternally inherited diabetes and deafness (MIDD) in Europe, and for all inherited mitochondrial respiratory chain disorders in the US. It has also been granted a rare pediatric disease designation in the US for the treatment of MELAS.

Sonlicromanol and other compounds from Khondrion's proprietary library have the potential to be developed for a wide range of diseases and conditions with the aim of benefiting patients whose daily lives are severely impacted by mitochondrial impairment. For more information visit www.khondrion.com.

About Primary Mitochondrial Disease

Mitochondrial disease occurs when mitochondria, found within all cells of the human body except erythrocytes, and responsible for producing the energy necessary for cells to function, are defective. This can result in a wide range of serious and debilitating illnesses occurring shortly after birth or later in life. Signs and symptoms of these can include cognitive problems, learning disabilities, blindness, deafness, heart failure, diabetes, fatigue, intolerance to exercise, muscle weakness and gait problems, and stunted growth.

Originally referred to as MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), primary mitochondrial disease associated with the m.3243A>G variant in the mitochondrial genome is now considered to include a spectrum of phenotypes including classic MELAS, MIDD syndrome (maternally inherited diabetes mellitus and deafness), MP (mixed

phenotypes) and CPEO (chronic progressive external ophthalmoplegia). Learn more: https://www.khondrion.com/melas-syndrome/.

Forward-looking statements

This press release may contain certain forward-looking statements regarding, among other things, the results, conduct, progress and timing of the company's clinical trials and presentation of data from clinical trials for sonlicromanol. Although the company believes its expectations are based on reasonable assumptions, all statements other than statements of historical fact included in this press release about future events are subject to (i) change without notice and (ii) factors beyond the company's control. These statements may include, without limitation, any statements preceded by, followed by or including words such as "target," "believe," "expect," "aim," "goal," "intend," "may," "anticipate," "foreseen," "estimate," "plan," "project," "will," "can have," "likely," "potential," "should," "would," "could" and other words and terms of similar meaning or the negative thereof. Forward-looking statements are subject to inherent risks and uncertainties beyond the company's control that could cause the company's actual results, performance or achievements to be materially different from the expected results, performance or achievements expressed or implied by such forward-looking statements. Except as required by law, the company assumes no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

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