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Mode of action of the mitochondrial clinical-stage drug candidate KH176: two birds, one stone

NIJMEGEN, The Netherlands – Khondrion, a leading clinical-stage pharmaceutical company focusing on small molecule therapeutics for mitochondrial diseases, today announced the publication of a scientific article reporting on the development and unique mode of action of KH176, a clinical-stage drug candidate for the treatment of mitochondrial diseases.

About the study

The work was carried out by the Khondrion R&D team in collaboration with Inoviem Scientific and the Radboud University Medical Center. The results were published in *Scientific Reports* (www.nature.com/articles/s41598-018-24900-3).

KH176 is an orally bio-available small molecule in development by Khondrion for the treatment of mitochondrial (-related) diseases. The present study reports on the early development and selection of KH176 as Khondrion's lead candidate and further explains its mode of action in primary cells obtained from mitochondrial patients. "Elevated Reactive Oxygen Species (ROS) levels and a high sensitivity to redox-stress are two frequent cellular consequences in mitochondrial disease. Interestingly, we could demonstrate in several patient-derived cells that KH176 is an attractive candidate to correct both pathological phenotypes, illustrating its unique potential for this group of patients" says Dr. Julien Beyrath, Chief Operating Officer at Khondrion and first author of the study. KH176 displays a dual mode of action, targeting both ROS and Redox disturbances. "Using cutting-edge target deconvolution technology, we could identify peroxiredoxin enzyme as the primary and novel target of KH176" added Dr. Beyrath. Research is ongoing to further unravel the exact molecular mechanism of interaction of KH176 with the peroxiredoxin enzyme, which will help the Khondrion R&D team to further improve their drug candidates. "The results presented highlight the potential of KH176 as a single molecule to be effective in a large group of heterogeneous mitochondrial diseases, but also other diseases with underlying ROS and Redox perturbations" adds Prof. dr. Jan Smeitink, CEO at Khondrion and last author of the study.

About KH176

KH176 was already shown to rescue specific pathological phenotypes in a relevant mouse model of Leigh disease, one of the most severe mitochondrial diseases ([De Haas, Scientific Reports, 2017 Sep 15;7\(1\):11733](https://doi.org/10.1038/s41598-017-11733-1)). Khondrion also reported that KH176 demonstrated a favorable pharmacokinetic profile and an acceptable safety profile in randomized, placebo-controlled, double blind Phase I clinical trials,

performed in healthy male volunteers ([Koene et al, Orphanet Journal of Rare Diseases, 2017 Oct 16;12\(1\):163](#)).

KH176 efficacy and safety have been evaluated in the KHENERGY study, a Phase II exploratory trial with oral KH176 in the m.3243A>G multisystem mitochondrial MELAS and MIDD syndromes and mixed phenotypes. Based on the outcome of the KHENERGY study ([see earlier press release](#)) the company is preparing for a pivotal program to confirm the potential benefits of KH176 in patients with mitochondrial disease.

About Khondrion

Khondrion is a leading clinical-stage pharmaceutical company focusing on developing small molecule therapeutics for mitochondrial (-related) diseases. The potential of several lead compounds to serve as new treatment modalities for mitochondrial disease is currently being explored. Khondrion's KH176 has been granted Orphan Drug Designation (ODD) for Leigh disease and MELAS syndrome in Europe and for all inherited mitochondrial respiratory chain disorders in the USA. Khondrion has established collaborations with patient organizations, patient advocacy groups, university expert centers and research groups around the world. The company is supported by the Dutch Foundations Energy4All, Join4Energy, Road4Energy, Ride4Kids, Tim Foundation, Zeldzame Ziekten Fonds, and National and European Governments. Khondrion has a strong intellectual property position protecting its emerging product portfolio via granted and multiple, broad patent applications. For more information, please visit www.khondrion.com

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements. All statements, other than statements of historical facts, contained in this press release, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Khondrion. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product development, including the uncertainties of clinical success and the timeline for the availability of KH176. While we may elect to update these forward-looking statements at some point in the future, we specifically disclaim any obligation to do so, even if our views change.

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