Press Release

Cardior's pioneering miRNA approach in heart failure endorsed by expert opinions in the *European Heart Journal*

- *First-ever development of an RNA therapeutic for heart failure*
- *Successful translation of unique scientific discovery into first-in-class clinical program*

Hanover, Germany, February 9, 2021 - Cardior Pharmaceuticals GmbH, a clinical-stage biotech company focused on the development of non-coding RNA (ncRNA) based therapeutics for patients with cardiovascular diseases, announced today that the Phase Ib results as well as preclinical and large-animal data of the Company's lead compound CDR132L were published alongside with two editorials from independent experts in the *European Heart Journal* Volume 42, Issue 3, January 14, 2021, an issue focusing on ischemic heart diseases.

Cardior's CDR132L: First-ever RNA-therapeutic addressing cardiovascular diseases advanced into the clinic

Andrew H. Baker[1] and Mauro Giacca[2] (doi.org/10.1093/eurheartj/ehaa967) review the Phase Ib data of Cardior's lead compound CDR132L, which were published in November 2020 in the *European Heart Journal* (http://doi.org/10.1093/eurheartj/ehaa898).

The authors note that to date no biologic treatment is available for cardiovascular diseases. With its leading-edge miRNA approach, Cardior is pioneering the development of first-in-class RNA-therapeutics for heart failure.

Cardior's concept is addressing a high unmet medical need: Over the last decade, it has become evident that non-coding nucleic acids (in particular miRNAs) play a fundamental role in the pathophysiology of heart failure. By targeting one specific miRNA, multiple genes in a given biological pathway can be regulated with a single intervention.

In the recent Phase Ib trial in heart failure patients, CDR132L met all endpoints and showed excellent tolerability and safety at all dose levels during the 120-day study period. No safety signals or unexpected adverse events were observed. Moreover, PK data confirmed strong dose-dependent linearity and specific target engagement. An exploratory analysis of multiple pharmacodynamic parameters, including measurement of NT-proBNP blood levels, showed beneficial effects on top of standard of care.

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Looking at the Phase Ib results, Baker and Giacca stress: “critically, plasma levels of miR-132-3p were dose-dependently reduced in patients receiving the drug.” While the study is “...underpowered for efficacy measures, there is striking safety and tolerability.” They underline that dose-dependent target reduction can be observed in the plasma.

Pre-clinical large animal data underline promising clinical findings

Yvan Devaux[3] and Lina Badimon[4] (doi.org/10.1093/eurheartj/ehaa870) emphasize that while many questions on miRNA therapeutics in heart failure are still to address (e.g. long-term effects, combination with existing treatments, etc.), Cardior has provided a first set of important data on miRNA therapeutics in the field.

According to the authors, the “potential of miRNAs to prevent, mitigate or restore cardiac dysfunction (...) is significant.” Moreover, they emphasize the great potential of miRNAs as biomarkers to monitor treatment efficacy.

In October 2020, Cardior had published pre-clinical large animal data of CDR132L in the *European Heart Journal* (doi:10.1093/eurheartj/ehaa791), demonstrating that repeated treatment with CDR132L is safe, improves cardiac function and reduces both ventricular as well as left atrial volumes in chronic heart failure. The results were obtained in a clinically relevant, post-myocardial infarction model in large animals. The data demonstrate that repeated monthly dosing of CDR132L is safe and adequate to provide clinically relevant exposure and therapeutic efficacy by improving both systolic and diastolic cardiac function.

The authors conclude that Cardior’s approach “... should be praised for translating a scientific discovery in the basic science laboratory, coming from the investigation of miR-132 and its functions, into a programme of drug development.”

Further clinical data expected

Both expert editorials endorse the importance of Cardior’s recent data for the development of a truly causal first-in-class biological treatment approach in heart failure.

The pre-clinical study helps to “cement another brick in the wall for the use of miRNAs to treat cardiovascular disease” (Devaux and Badimon), while the Phase Ib data set “...represents a considerable advance in the field of miRNA therapeutics in cardiovascular disease” (Baker and Giacca).

Cardior plans to initiate a clinical Phase II trial with CDR132L later this year.

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About CDR132L

CDR132L is an antisense oligonucleotide developed by Cardior Pharmaceuticals inhibiting the microRNA-132 (miR-132), a non-coding microRNA that regulates cardiac hypertrophy and remodeling in cardiomyocytes by targeting well-defined pathways.

miR-132 is a regulatory master switch to control cardiac function and a promising, causal therapeutic target in heart failure therapy. Expression of miR-132 is increased in various pathological cardiac conditions in both animals and humans, and previous preclinical studies have shown that miR-132 is essential for driving the pathological growth of cardiomyocytes.

In a randomized, double-blind, placebo-controlled, dose-escalating Phase Ib study CDR132L showed excellent safety and tolerability, linear dose-dependent pharmacokinetic (PK) and promising pharmacodynamic (PD) properties in heart failure (HF) patients on guideline directed medication. The study design combined dose escalation with repeat dosing (day 1 and 28) at 4 dose levels. 28 patients received CDR132L or placebo (5:2 randomized in 4 cohorts) via short-term (15 min.) intravenous infusions.

About Cardior Pharmaceuticals

Cardior Pharmaceuticals is a clinical-stage, privately held German biopharmaceutical company pioneering the development of curative and preventive heart failure therapeutics based on non-coding RNAs (ncRNAs). Cardior's therapeutic approach is using distinctive ncRNA signatures driving the molecular reprogramming that causes maladaptive remodeling and heart failure. Drug candidates developed by Cardior represent first-in-class ncRNA therapeutics and diagnostics for patients with myocardial infarction and various forms of heart failure. Founded in 2016 based on the work of cardiologist Prof. Dr. Dr. Thomas Thum of Hannover Medical School, the Company is funded by a consortium of leading investors: LSP, BioMedPartners, Boehringer Ingelheim Venture Fund (BIVF), Bristol-Myers Squibb (BMS) and High-Tech Gründerfonds (HTGF).

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