FOR IMMEDIATE RELEASE AFTER LANCET EMBARGO

Cardiawave announces the publication in *The Lancet* of First-In-Human clinical studies results with 40 aortic stenosis patients treated with its innovative Non-Invasive Ultrasound Therapy (NIUT)

- Non-Invasive Ultrasound Therapy (NIUT) is feasible and safe.
- Hemodynamic and clinical improvements statistically demonstrated in high-risk patients with calcific aortic stenosis (CAS).
- Patients experienced a considerable improvement in their quality of life.
- A valve repair option bringing a new medical breakthrough to millions of people suffering from CAS in the world.
- These results and the completion of patients' enrolment in the pivotal study pave the way for CE marking of the device.
- Major milestone reached : successful treatment of 100 patients at 12 investigational centers in 4 countries.

Levallois-Perret, France, 14-Nov-2023 – Cardiawave SA, a French Medtech which has developed an innovative Non-Invasive focused Ultrasound Therapy device for the treatment of calcific aortic stenosis, announced today the publication of results from its First-In-Human (FIH) clinical studies on 40 patients suffering from CAS treated with its NIUT in *The* Lancet and the completion of the enrollment of 60 patients in its "Valvosoft® pivotal study".

First-In-Human « Valvosoft® FIM Study » results published in *The Lancet:* *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01518-0/fulltext*

These clinical studies' series entitled "*Prospective, controlled, single-arm clinical investigation for the treatment of subjects with severe symptomatic aortic valve stenosis using Valvosoft® Pulsed Cavitational Ultrasound Therapy (PCUT) – First-In-Man*" (Coordinating Investigator: Prof. Emmanuel Messas, MD, PhD, FESC, Cardiologist at Hôpital Georges Pompidou AP-HP in Paris, France) enrolled 40 patients with severe symptomatic aortic valve stenosis at 3 clinical sites in France (Hôpital Européen Georges Pompidou, AP-HP, Paris), in the Netherlands (Amphia Hospital, Breda), and in Serbia (University Clinical Center of Serbia, Belgrade). The patients were treated with Cardiawave's NIUT investigational device in one session. Follow-ups were scheduled at 1, 3, 6, 12, and 24 months. Six-month data are reported in the publication.

The primary endpoints were met with no procedure-related mortality through 30 days and improved valve function. No procedure-related mortality occurred; furthermore, no life-threatening or cerebrovascular events were reported. Improved valve function was confirmed at 6 months, reflected by a 10% increase in mean aortic valve area and by quality-of-life improvements.

The New York Heart Association (NYHA) score improved or stabilized in 96% of patients (n=24), and the mean Kansas City Cardiomyopathy Questionnaire (KCCQ) score improved by 33%.

"*Results from this FIH series with a cohort of very frail patients suggest that the use of Non-Invasive Ultrasound Therapy (NIUT) is feasible and safe, and efficient with statistically significant improvements of hemodynamic and clinical parameters in high-risk patients with calcific aortic stenosis (CAS)*." said

Professor Roxana Mehran, MD, PhD, FACC, FACP, FCCP, FESC, FAHA, FSCAI, Cardiologist, Mount Sinai, New York, NY, USA and member of Cardiawave scientific advisory board. "*Clinically, the patients experienced a considerable improvement in their clinical status suggesting a better quality of life. These early findings can represent a change in the paradigm of CAS treatment especially for patients who have no other options. I am encouraged by the momentum of these study results as I anticipate that this therapy potentially brings a new medical breakthrough to many patients suffering from CAS in the world.*"

End of patients' enrollment in "Valvosoft® Pivotal Study"

In June 2022, following the positive results of our FIH clinical studies, Cardiawave started a pivotal study on severe symptomatic aortic valve stenosis patients who refuse (in Germany and Netherland) or were not recommended for valve replacement. In July 2023, Cardiawave successfully completed the patient enrolment with no procedure or device-related mortality up to 30 days. The study, entitled "Prospective, Single-arm Pivotal Study for the Treatment of Subjects with Severe Symptomatic Calcific Aortic Valve Stenosis Using Valvosoft® Non-Invasive Ultrasound Therapy", successfully enrolled 60 patients at 11 clinical sites in France, Germany and the Netherlands and marks a significant milestone in the development of Cardiawave's medical advances, paving the way for CE marking of the device.

Cardiawave would like to express its gratitude to the patients who took part in this clinical study, and to the medical teams and researchers who helped make it possible. The company is committed to continuing its efforts to advance healthcare in the field of cardiology and improve patients' quality of life.

What's next?

After the successful treatment of 100 patients at 12 investigational centers in 4 countries, Cardiawave is preparing a Series B financing round which will enable the company to prepare the scale up, the market access in Europe and the launch of its clinical developments in the United States of America as part of the pre-market approval by the Food and Drug Administration (FDA).

About Valvosoft®

This is a non-invasive ultrasound therapy investigational medical device for the treatment of calcific aortic stenosis developed by Cardiawave. This device uses a new and unique non-invasive transthoracic ultrasound technology that delivers shockwaves on the aortic valve through the cavitation phenomenon. Ultrasound softens the tissue, restores leaflet mobility, and enables a wider opening of the valve. It is currently undergoing clinical investigations for safety and efficacy. It has not yet received any marketing authorization (e.g. CE Marking) and is intended exclusively for clinical investigations.

Cardiawave has developed its new breakthrough technology following the work of the prestigious French academic laboratories Institut Langevin (INSERM/CNRS/ESPCI) and Physics for Medicine Paris (INSERM/CNRS/ESPCI/PSL). This non-invasive treatment of aortic stenosis combines therapeutic ultrasound, robotics, and ultrasound imaging. All software and most hardware components have been developed in-house thanks to the unique know-how of Cardiawave and its academic partners.

About CALCIFIC AORTIC STENOSIS

Calcific aortic stenosis (CAS) is a degenerative and potentially life-threatening condition, caused by calcium buildup which prevents the aortic valve from fully opening. Aortic Stenosis (AS) evolves over time leading to heart failure and increases the risk of sudden death during its final stage (severe & symptomatic stenosis). AS has become a public health issue as the pathology affects between 1,7 and 12,4% of subjects over 75 years old (sources: Durko AP, et al. Annual number of candidates for transcatheter aortic valve implantation per country: current

estimates and future projections. European Heart Journal. July 01, 2018; 39(28):2635-2642. (DOI: 10.1093/eurheartj/ehy107); Lindman B, et al. Calcific Aortic Stenosis. Nature Reviews Disease Primers 2, Article number: 16006. March 03, 2016. (DOI: 10.1038/nrdp.2016.6); Osnabrugge R., et al. Aortic Stenosis in the Elderly: Disease Prevalence and Number of Candidates for Transcatheter Aortic Valve Replacement: A Meta-Analysis and Modeling Study. Journal of American College of Cardiology, Volume 62, Issue 11, Pages 1013-1014. September 2013. (DOI: 10.1016/j.jacc.2013.05.015). With age, the aortic valve calcifies, becomes more rigid and narrow, and no longer opens properly leading to poor blood circulation.

AS can be mild, moderate, and severe. 2 million people are estimated to suffer from severe AS in Europe and in the USA, of whom 500,000 per year benefit from Transcatheter Aortic Valve Replacement (TAVR) or open-heart surgery. 1.5 million patients remain untreated and face a low life expectancy of 2 to 5 years. Around 3 million further patients suffer from moderate AS for whom there is no early treatment.

About CARDIAWAVE

Cardiawave has developed a Non-Invasive Ultrasound Therapy (NIUT) medical device for the treatment of valvular heart diseases, and in particular, CAS, the most prevalent heart valve disease in adults and one of the most common causes of cardiovascular mortality worldwide. Based near Paris, Cardiawave is a member of the national research consortium RHU Stop-AS, and has EN ISO 13485:2016 certification since 2019. Cardiawave employs 30 people and has secured over 29M€ in funding since its creation in 2014. This project was supported by the Program "Investissements d'Avenir" as part of the World Innovation Competition. It also benefited from state aid managed by the National Research Agency under the references ANR-16-RHUS-0003_STOP-AS and ANR-17-CE19-0019-03 and the Horizon 2020 SME instruments program of the European Commission (reference no. 829492). Cardiawave is a winner of the French Tech Health 20 programme and a member of La French Care since 2023.

Learn more: www.cardiawave.com

Winner 2023 French Tech Health 20

French Care Member

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