# Celsion Announces Publication of ThermoDox® Study Results in Radiology

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*Publication Highlights Phase I Data Supporting Safety and Feasibility of Treatment with ThermoDox® and Non-Invasive, Focused Ultrasound*

*University of Oxford's Findings Provide Additional Independent Evidence of ThermoDox's Unique and Highly Effective Anti-Cancer Mechanism*

LAWRENCEVILLE, N.J, Jan. 17, 2019 (GLOBE NEWSWIRE) -- Celsion Corporation(NASDAQ: CLSN), an oncology drug development company, today announced that results from the Phase I TARDOX trial of ThermoDox®conducted at the University of Oxford, United Kingdom, were published in the peer-reviewed journal, *Radiology*. The TARDOX trial evaluated the safety and efficacy of ThermoDox®, Celsion's proprietary heat-activated liposomal encapsulation of doxorubicin, along with focused ultrasound for the treatment of liver cancer. The article, titled, "Focused Ultrasound Hyperthermia for Targeted Drug Release from Thermosensitive Liposomes: Results from a Phase I Trial," included an evaluation of the TARDOX results and the safety, efficacy and utility of treatment with ThermoDox® plus targeted, non-invasive hyperthermic ultrasound in patients with solid liver tumors, with treatment plans based on patient-specific modeling.

"The findings published in *Radiology* serve as a companion paper to the groundbreaking work published by Lyons et al in Lancet Oncology in July 2018. This work by the TARDOX team at the Oxford University Institute of Biomedical Engineering clearly demonstrated the local activity of ThermoDox® in liver cancer. This is the first published study to evaluate ThermoDox® as an effective therapeutic when combined with high-intensity focused ultrasound (HIFU). The *Radiology* paper is also accompanied by an editorial which highlights the significance of utilizing HIFU and ThermoDox®. Namely, that high concentrations of important drugs such as doxorubicin – through ThermoDox - can be delivered locally and effectively," said Nicholas Borys, M.D., Celsion's senior vice president and chief medical officer." While further studies are warranted, the medical community has advocated for the use of ThermoDox® with focused ultrasound for some time, and these observations support the potential for focused ultrasound to expand the use of ThermoDox® to the treatment of other types of cancer."

A lysolipid thermally sensitive liposome encapsulating the chemotherapy agent, doxorubicin, ThermoDox®is designed to release targeted levels of doxorubicin into and around liver tumors with heat activation. The Phase I TARDOX study demonstrated that focused ultrasound exposure with ThermoDox® resulted in increased chemotherapy concentrations within liver tumors that were an average of 3.7 times greater than preheating levels across all 10 patients in the study.

"This latest publication of ThermoDox ® clinical data emphasizes the significance and utility of its thermally activated delivery system and the high level of interest and support from the medical community for improved, targeted delivery of therapeutically potent levels of chemotherapy in patients with primary liver cancer, and potentially other cancers. Consistent with the US National Institutes of Health's findings, Oxford's clinical results add to the independent evidence of ThermoDox®'s unique and potent anti-cancer mechanism of action," said Michael H. Tardugno, Celsion's chairman, president and chief executive officer. "Moreover, the positive findings from the TARDOX study showed the viability of focused ultrasound to deliver potent levels of doxorubicin with ThermoDox®, suggesting that ThermoDox® could also be successful when used in combination with other heating mechanisms, beyond radiofrequency ablation (RFA). This highly reassuring research fully supports our robust clinical development program for ThermoDox® in combination with RFA. We are looking forward to the first of two planned interim efficacy analyses from our ongoing Phase III OPTIMA study in 556 patients in mid-2019."

The Phase I TARDOX study evaluated patients with inoperable primary or secondary liver tumors who had previously received chemotherapy. In this trial, 10 patients received a single intravenous dose of 50 mg/m$^2$ of ThermoDox®, and ultrasonic heating of target tumors was monitored in six participants using a minimally invasive temperature sensor, while four patients were treated without real-time thermometry. Safety was assessed by analysis of magnetic resonance imaging (MRI) and biopsy specimens for evidence of thermal ablation, as well as adverse event monitoring. There was no evidence of focused ultrasound-related adverse effects, including thermal ablation.

Numerous studies have demonstrated that focused ultrasound can be used to generate mild heating to facilitate the release of drug cargoes from thermosensitive liposomes (TSLs). We believe the TARDOX study is the world's first Phase I clinical trial aimed at evaluating the effect of doxorubicin released from TSLs after focused ultrasound–induced mild hyperthermia. The study presents a model for predicting the focused ultrasound treatment parameters needed to attain mild hyperthermia and facilitate doxorubicin release from TSLs. This model may improve the current clinical use of hyperthermia by providing an alternative strategy for treatment planning based on a thermal model rather than actual thermometry, which is more invasive.

For all participants, CT images were used with the patient-specific hyperthermia model in order to define focused ultrasound treatment plans. Feasibility was assessed by comparing model-prescribed focused ultrasound powers to those implemented for treatment. The mean difference between predicted and implemented treatment powers was -0.1 W ± 17.7 SD. We believe this is a meaningful initial demonstration of the model providing accurate, successful treatment parameters. In addition, these observations support the potential for non-invasive hyperthermic ultrasound to expand the use of ThermoDox® to the treatment of other types of cancer.

The TARDOX study was carried out as a multi-disciplinary collaboration between Celsion, the Oxford University Institute of Biomedical Engineering, the Oncology Clinical Trials Office (OCTO) and the Oxford University Hospitals NHS Foundation Trust.

**About ThermoDox®**

Celsion's most advanced program is a heat-mediated, tumor-targeting drug delivery technology that employs a novel heat-sensitive liposome

engineered to address a range of difficult-to-treat cancers. The first application of this platform is ThermoDox®, a lyso-thermosensitive liposomal doxorubicin (LTLD), whose novel mechanism of action delivers high concentrations of doxorubicin to a region targeted with the application of localized heat at 40°C, just above body temperature. In one of its most advanced applications, ThermoDox®, when combined with radiofrequency thermal ablation (RFA), has the potential to address a range of cancers. For example, RFA in combination with ThermoDox® has been shown to expand the "treatment zone" with a margin of highly concentrated chemotherapy when treating individual primary liver cancer lesions. The goal of this application is to significantly improve efficacy.

Celsion's LTLD technology leverages two mechanisms of tumor biology to deliver higher concentrations of drug directly to the tumor site. The first: Rapidly growing tumors have leaky vasculature, which is permeable to liposomes and enables their accumulation within tumors. Leaky vasculature influences a number of factors within the tumor, including the access of therapeutic agents to tumor cells. Administered intravenously, LTLD is engineered to allow significant accumulation of liposomes at the tumor site at the time of radiofrequency ablation as these liposomes recirculate in the blood stream. The second: When the tumor tissue is heated to a temperature of 40°C or greater, the heat-sensitive liposome rapidly changes structure and the liposomal membrane selectively dissolves, creating openings that release the chemotherapeutic agent directly into the tumor and into the surrounding vasculature. Drug concentration increases as a function of the accumulation of liposomes at the tumor site, but only where the heat is present. This method targets only the tumor and the area related to tumor invasion, supporting precise drug targeting.

**About the OPTIMA Study**

The Phase III OPTIMA Study has enrolled 556 patients in over 60 clinical sites in the United States, Europe, China and Asia Pacific, and will evaluate ThermoDox® in combination with optimized RFA, which was standardized to a minimum of 45 minutes across all investigators and clinical sites for treating lesions three to seven centimeters, versus optimized RFA alone. The primary endpoint for the trial is overall survival. The OPTIMA Study is supplemented by post-hoc analyses of data from the Company's 701-patient HEAT Study in which optimized RFA demonstrated the potential to significantly improve survival when combined with ThermoDox®. The OPTIMA Study's statistical plan calls for two interim efficacy analyses by an independent Data Monitoring Committee.

**About Celsion Corporation**

Celsion is a fully-integrated oncology company focused on developing a portfolio of innovative cancer treatments, including directed chemotherapies, immunotherapies and RNA- or DNA-based therapies. The Company's lead program is ThermoDox®, a proprietary heat-activated liposomal encapsulation of doxorubicin, currently in Phase III development for the treatment of primary liver cancer. The pipeline also includes GEN-1, a DNA-based immunotherapy for the localized treatment of ovarian and brain cancers. Celsion has two platform technologies for the development of novel nucleic acid-based immunotherapies and other anti-cancer DNA or RNA therapies. For more information on Celsion, visit our website: http://www.celsion.com. (CLSN-LTSL/ThermoDox® CLSN-Optima Study/HCC)

*Celsion wishes to inform readers that forward-looking statements in this release are made pursuant to the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Readers are cautioned that such forward-looking statements involve risks and uncertainties including, without limitation, unforeseen changes in the course of research and development activities and in clinical trials; the uncertainties of and difficulties in analyzing interim clinical data; the significant expense, time, and risk of failure of conducting clinical trials; the need for Celsion to evaluate its future development plans; possible acquisitions or licenses of other technologies, assets or businesses; possible actions by customers, suppliers, competitors, regulatory authorities; and other risks detailed from time to time in Celsion's periodic reports and prospectuses filed with the Securities and Exchange Commission. Celsion assumes no obligation to update or supplement forward-looking statements that become untrue because of subsequent events, new information or otherwise.*



**Investor Contact**

**Argot Partners**

Sam Martin

212-600-1902

Sam@argotpartners.com

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