Cryoablation of Low-Risk Breast Cancers less than 1.5 cm: An evaluation of local recurrence (Ice3 Trial) – ICMBC-02

Study Plan- Synopsis

Study Title	Cryoablation of Low-Risk Breast Cancers less than 1.5 cm: An evaluation of local recurrence (Ice3 Trial)
Investigational Device	PROSENSE™
Study Sites and Participants	212 subjects/ 19 sites
Device Description	IceCure Medical's PROSENSE™ cryogenic system (also branded as ICESENSE3™) is intended for cryogenic destruction of tissue (utilizes Liquid Nitrogen) during surgical procedures (minimally invasive image-guided), by the application of extreme cold temperatures. The PROSENSE™ system has FDA clearance (K183213) for use as a cryosurgical tool in the fields of general surgery (including breast fibroadenomas), dermatology, neurology, thoracic surgery, ENT, gynecology, oncology, proctology, and urology.
Study Design	Multi-centered, single arm, non-randomized clinical trial. Patients will undergo imaging by mammography, ultrasound and breast MRI (optional) pre-registration to ensure eligibility. All fully eligible and registered patients will then be treated with cryoablation therapy followed by 6 month and annual mammograms and physical examinations for 5 years post treatment.
Study Objectives	The goal of this study is to evaluate the safety and efficacy, in terms of Ipsilateral Breast Tumor Recurrence (IBTR) rate of cryoablation using IceCure medical's PROSENSE™ device for the treatment of low-risk early breast cancer in women 50 years or older.
Study Endpoints	**Primary endpoint:** Local Ipsilateral Breast Tumor Recurrence (IBTR) rate. **Secondary endpoints:** • Complete ablation of primary tumor rates up to 60 months after cryoablation. • Improvement or maintenance of subject's quality of life at 6 months compared to baseline.

	• Breast cosmetics satisfaction. • Regional Invasive breast tumor recurrence rate. • Distant metastases rate including contralateral Breast cancer. • Disease–free Survival (DFS) from date of complete ablation of the primary tumor, until the first disease event where the disease event is defined as local (DCIS or invasive), regional, or distant breast cancer recurrence, second primary cancer, DCIS or invasive contralateral breast cancer, or death due to any cause. • Overall survival from the date of the cryoablation until the date of death from any cause or up to the 60 months follow up visit. • Breast Cancer Survival from the date of cryoablation until the date of death from breast cancer or up to the 60 months follow-up visit. Subjects who died without a specified cause will be considered as events (i.e., due to breast cancer). • Adverse events related to study device or procedure rate.
Study Population	Women aged 50 or older, with low-risk breast carcinoma, less or equal to 1.5 cm in diameter, will be enrolled into the study.
Main Eligibility Criteria	1. Diagnosis of invasive ductal breast carcinoma by core needle biopsy, meeting the following criteria: a. Unifocal primary disease b. Tumor size <1.5 cm in greatest diameter c. Nottingham grade 1-2. d. Estrogen receptor positive, and or progesterone receptor positive, HER2 negative, 2. Age ≥ 50 (Local IRB), Age ≥ 60 (WCG IRB) 3. Breast size adequate for safe cryoablation. 4. Lesion must be sonographically visible at the time of treatment. 5. History of previously treated ipsilateral or contralateral breast carcinoma is not an exclusion criteria if the investigator is certain newly diagnosed carcinoma is new unifocal primary tumor.

Exclusion Criteria	1. Presence of lobular carcinoma 2. Presence of luminal B pathology 3. Nottingham score of 3 4. Presence of microinvasion or invasive breast carcinoma with extensive intraductal component (EIC) 5. Presence of multifocal and/or multicentric in breast cancer 6. Presence of multifocal calcifications 7. Presence of prior or concurrent neoadjuvant chemotherapy for breast cancer 8. Presence of prior en bloc open surgical biopsy and/or lumpectomy for diagnosis/treatment of the index breast cancer 9. Patient that is not suitable to cryoablation procedure according to the physician opinion 10. ER AND PR negative, or Her2 positive noted on pre-cryo biopsy
Statistical analysis-General considerations	Statistical analyses will be performed using SAS® v9.3 or higher (SAS Institute, Cary NC, USA). Statistical tests performed will be two-sided. The required significance level of findings will be equal to or lower than 5%. Where the confidence level will be 95%. Baseline values are defined as the last valid value prior to study treatment start. All statistical analyses of safety and performance measures will be descriptive in nature. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage. Confidence intervals will be provided where relevant. The study results will be discussed comparatively to data published of similar products.