DE NOVO CLASSIFICATION REQUEST FOR

PROSENSE CRYOABLATION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Cryoablation device for local treatment of low-risk breast cancer**. A cryoablation device for local treatment of low-risk breast cancer is a prescription device that uses cold temperatures to destroy a breast tumor and its surrounding tissue. The device is intended as a local treatment and may be used with adjuvant therapies (e.g., endocrine therapy, radiation therapy) to reduce the risk of local disease progression. The device is intended for use in patients with a well-defined solid tumor (e.g., invasive ductal carcinoma) and with low risk of recurrence and metastasis, as determined by clinical risk factors consistent with the indications for use. The device is not intended to treat breast cancers with high risk of local recurrence (e.g., lobular carcinoma), patients with aggressive forms of breast cancer (e.g., breast cancers with inflammatory features), or patients in whom targeted systemic therapy is indicated.

NEW REGULATION NUMBER: 21 CFR 878.4355

CLASSIFICATION: Class II

PRODUCT CODE: QXW

BACKGROUND

DEVICE NAME: ProSense Cryoablation System

SUBMISSION NUMBER: DEN220077

DATE DE NOVO RECEIVED: October 20, 2022

SPONSOR INFORMATION:

IceCure Medical
7 Ha'Eshel St., P.O. Box 3163
Caesarea, Israel 3079504

INDICATIONS FOR USE

The ProSense cryoablation system is indicated as follows:

ProSense cryoablation system is indicated for the local treatment of breast cancer in patients ≥70 years of age with biologically low-risk tumors ≤1.5 cm in size and treated with adjuvant endocrine therapy, including patients not suitable for surgery for breast cancer treatment.

Biologically low-risk breast cancer is defined as unifocal tumor, size ≤1.5 cm, ER-positive, PR-positive, HER2-negative, Ki-67<15% and/or genomic testing indicative of low-risk breast cancer, infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).

LIMITATIONS

ProSense's safety and effectiveness for breast cancer treatment were evaluated in a single-arm trial with 5 years follow up. Breast cancer treatment outcomes following cyrotherapy have not been studied in direct comparison to surgical excision (e.g., lumpectomy).

Breast cancer treatment outcomes including recurrence rates, disease-free survival, and overall survival after use of this device are unknown beyond 5 years.

Unlike surgical removal of the tumor (e.g., lumpectomy) where there is a specimen for pathology to confirm whether the tumor was completely removed, cryoablation relies on imaging to determine if the tumor was destroyed. However, the exact boundaries may not be visible on imaging which can result in incomplete destruction of the tumor.

The recurrence rate is being further evaluated in a larger patient population through an ongoing post-market study.

ProSense cryoablation system is not intended as a treatment for recurrent breast cancer.

ProSense cryoablation system is not intended for patients in whom neo-adjuvant chemotherapy and/or biological therapy or other targeted neo-therapies apart from endocrine therapy are indicated.

ProSense cryoablation system is not intended as a treatment for breast cancers with inflammatory features.

Only patients with adequate breast size can undergo safe breast cancer treatment with ProSense cryoablation system.

Practices of cryoablation for women with breast implants have not been established. For patients with breast implants, you must document that adequate distance exists between the lesion and the implant to ensure that the ablated lesion will not contact or jeopardize the implant, and there is enough space to create the required margins.

The sale, distribution, and use of the ProSense cryoablation system are restricted to prescription use in accordance with 21 CFR 801.109.

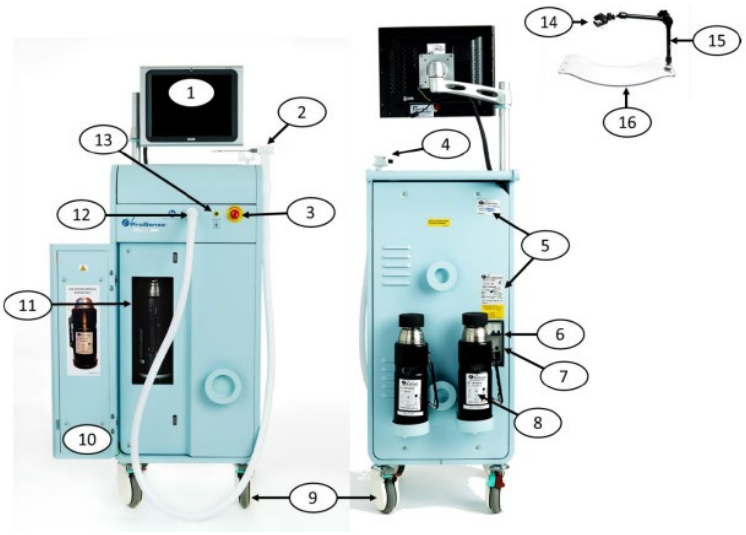
PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The ProSense cryoablation system (**Figure 1**), previously cleared in K183213, is intended to destroy tissue by cooling the selected target to extremely low temperatures using pressurized liquid nitrogen and a single-use, disposable cryoprobe (**Figure 2**). Depending on the intended surgical use, the user can select from an array of cryoprobes with different gauges (10 G or 13 G), ice ball shapes (spherical or elliptical), and shaft lengths (ranging 124-185 mm). For the intended use in this De Novo submission, local treatment of breast cancer, a 10 G cryoprobe with elliptical ice ball shape and 140 mm shaft length (FAP7200000) is the only cryoprobe validated for use.

During a cryoablation procedure for the local treatment of breast cancer, the cryoprobe is inserted (with or without an introducer) through a small opening in the skin created by a surgical scalpel and advanced through underlying breast tissue, directly into the cancerous tumor. Under ultrasound visualization, the cryoprobe cooling zone is centered in all three planes of the lesion (sagittal, transverse, and anterior-posterior) based upon a calculation that relates the specifications of the selected cryoprobe with the tumor and anatomical site dimensions. The cancerous tissue is then frozen to sub-zero temperatures by the liquid nitrogen ice ball, which is formed on the cryoprobe around the cooling zone center. The cooling zone center of the cryoprobes reaches a minimum of -170°C.

The device has a manual mode and an automatic mode which determine the number and duration of freeze and thaw steps. The quick-freezing cycle causes ice crystal formation within the affected cells and consequent cell expansion, effectively destroying the tissue. Tumors are typically ablated in two freeze-thaw cycles, achieving a core temperature of -150°C or lower. Default treatment times are 9 minutes for each freeze cycle and 8 minutes for the thaw cycle. However, since the ice ball growth varies from patient to patient, treatment times can be adjusted at the operator's discretion. The system allows up to seven freeze-thaw steps. After completion of the procedure, the probe is extracted at a probe tip temperature no higher than 35°C. The procedure for local treatment of breast cancer typically takes 20 – 40 minutes.



1. Touch screen
2. Cryohandle
3. Emergency Stop button
4. Cryoprobe cradle
5. System labels
6. ON-OFF switch
7. Potential Equalization pin (POAG)
8. Dewar
9. Rollers
10. Dewar positioning door/Elevator door
11. Dewar elevator compartment
12. Flexible hose connection
13. Temperature sensor port
14. Adjustable clamp
15. Holder adjustable arm
16. Holder base

Figure 1. Front and back view of the ProSense cryoablation system with numbered components.

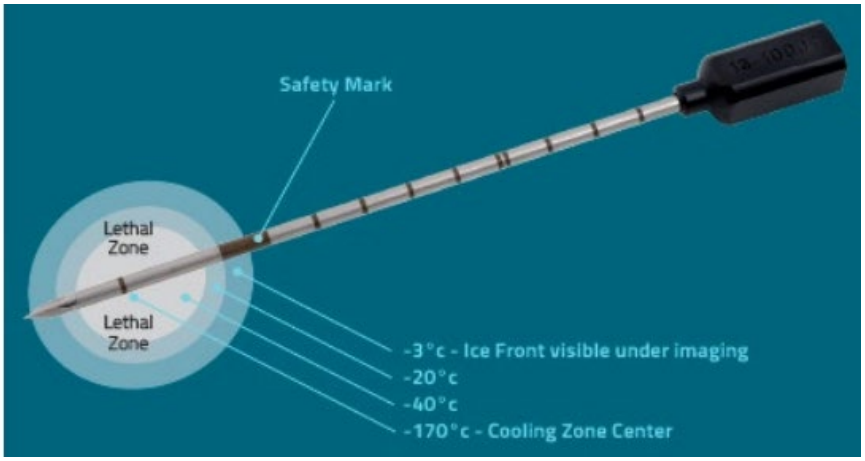


Figure 2. Schematic of the cryoprobe.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The biocompatibility evaluation of patient contacting materials of the ProSense cryoablation system and its accessories was conducted in accordance with FDA's "Guidance for Industry and Food and Drug Administration Staff: Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'" Biocompatibility data was leveraged from prior 510(k) clearances for the same device. No new biocompatibility data was evaluated in the De Novo submission.

STERILIZATION

The ProSense cryoablation system and its accessories (probes, introducers and temperature sensor) are all sterilized utilizing an Ethylene Oxide sterilization cycle validated in accordance with ISO 11135 - Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization. The shelf-life of the cryoablation system is 5 years. Shelf-life was established based on a study including barrier integrity physical testing – Dye; Barrier integrity physical testing – Peel (Tensile seal strength test); and Visual examination to evaluate the barrier impermeability and continuous properties of the seals of the proposed packaging materials. Package integrity was maintained for 5 years. Sterilization and shelf-life testing was leveraged from prior 510(k) clearances for the same device. No new sterilization or shelf-life data was evaluated in the De Novo submission.

SOFTWARE

Software documentation for a Moderate Level of Concern software was developed and in compliance with "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Software documentation was leveraged from prior 510(k) clearances for the same device. No new software documentation was evaluated in the De Novo submission.

ELECTROMAGNETIC COMPATIBILITY (EMC) & ELECTRICAL SAFETY

Electromagnetic compatibility (EMC) and electrical safety (ES) of the IceCure cryoablation system were tested and determined to be compliant with the following standards:

- ES60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012(Consolidated Text) Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (IEC 60601-1:2005, MOD).
- IEC 60601-1-2 Edition 4.0 2014-02 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests.

Electromagnetic compatibility and electrical safety testing were leveraged from prior 510(k) clearances for the same device. No new EMC and ES data was evaluated in the De Novo submission.

BENCH TESTING

Bench testing was conducted to demonstrate that the device meets cryogen pressure and flow rate specifications with the intended cryogen type and the dimensions of the active part of the applicator. Bench testing was also provided to demonstrate that the cryoprobe meets temperature specifications for freezing and thawing and meets freezing performance specifications under the anticipated load in a representative test medium. Bench testing was leveraged from prior 510(k) clearances for the same device. No new bench testing was evaluated in the De Novo submission.

CLINICAL PERFORMANCE TESTING

Background Clinical Data

Several studies in published literature were submitted and evaluated as background to the pivotal study (referred to herein as 'ICE3 trial' or 'ICE3 study'). In these studies, breast cancer patients were treated with cryoablation and underwent surgical resection within 30 days to conduct pathology assessment of the resected specimen and evaluate the rate of complete ablation (referred to herein as '*ablate and resect*' studies). The studies are summarized in **Table 1**.

The studies evaluated cryoablation of tumors up to 2 cm in size in patients with invasive ductal carcinoma; a small portion of patients had ductal carcinoma in situ (DCIS), lobular carcinoma, colloid carcinoma, and medullary carcinoma. The total number of patients evaluated in these studies ranged from 9 to 99. The studies used argon gas-based cryoablation systems to apply a double freeze/thaw cycle, with each phase of the cycle typically lasting 6-10 minutes. Note, the ProSense cryoablation system (liquid nitrogen-based system) was not used in these background studies. Typical procedure times were 30-40 minutes.

These articles reported effectiveness rates of complete tumor necrosis ranging from 76% to 100%. The likelihood of cryoablation success correlated with tumor size and histology, and incomplete ablation of the surrounding extensive intraductal component was noted. For example, in the American College of Surgeons Oncology Group study (ACOSOG Z-1072), which contained the most patients, the results showed successful ablation in 75.9% of cancers eligible for evaluation (66 of 87) and residual invasive breast cancer and/or DCIS in 24.1% (21 of 87). When multifocal disease outside of the targeted cryoablation zone was not defined as an ablation failure, 92% (80 of 87) of the treated tumors had successful cryoablation. There was 100% ablation success in tumors <1.0 cm compared with 77.4% success in tumors >1.0 cm. This study also evaluated the accuracy of breast MRI to assess the residual tumor two weeks after cryoablation. When MRI was used to determine residual invasive breast cancer or DCIS, the negative predictive value of MRI (success in detection of no residual cancer when pathology results were negative) was 81.2% (90% CI: 71.4-88.8%). The reported limitations across the studies included underestimation of tumor margin and tumor extent with imaging methods prior to conducting the cryoablation procedure.

Table 1. Summary of ablate and resect literature studies referenced by IceCure Medical as background data to the ICE3 trial.

Study type	Feasibility
Study method	Ablate and resect
Device	Argon gas-based cryoablation systems (e.g., Visica Cryotherapy System by Sanarus Medical); the ProSense system (liquid nitrogen-based) was not used
Number of patients	Between 9 and 99 depending on the study cohort
Tumor size	Up to 2 cm (cohorts <1.0 cm, ≤1.6 cm, ≤1.8 cm, and ≤2.0 cm)

Breast cancer type	Invasive ductal breast cancer; some patients had medullary or colloid carcinoma, lobular carcinoma or abundant DCIS
Cryoablation method	Double freeze/thaw cycle
Total procedure time	30-40 minutes
Time to resection	14-30 days after cryoablation
Major findings	76-100% complete tumor necrosis; some patients had residual invasive breast cancer or DCIS surrounding the ablation zone
Key safety findings	No significant complications reported, no patients needed postprocedural narcotic pain medications
Reported limitations	Underestimation of tumor margin and tumor extent with imaging methods prior to conducting the cryoablation procedure

ICE3 Pivotal Study

IceCure Medical conducted a pivotal study entitled "*Cryoablation of Low Risk Breast Cancers less than 1.5 cm: An evaluation of local recurrence (ICE3 Trial).*" The ICE3 trial was a multi-center, non-randomized, single-arm study conducted across 19 U.S. clinical sites. The objective of the study was to evaluate the safety and effectiveness of cryoablation using the ProSense cryoablation system for the treatment of early-stage breast cancer, in lieu of lumpectomy, and its impact on local recurrence at 5 years follow up.

Enrollment Criteria

The study enrolled women with early stage, low risk breast cancer as described in the Key Inclusion and Exclusion Criteria presented in **Table 2**. Patients were not required to receive endocrine therapy (also known as hormone therapy), radiation therapy, or chemotherapy, and received these adjuvant therapies at the discretion of the treating physicians. The clinical study protocol was modified during study enrollment, including revisions to the eligibility criteria*.

Table 2. Key enrollment criteria for the ICE3 pivotal clinical study.

Key Inclusion Criteria	Key Exclusion 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; nuclear and mitotic scores ≤ 2* d. ER positive and/or PR positive e. HER2 negative f. Lymph node negative (N0) 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	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

* Ki-67<14% was initially defined as an inclusion criterion in the ICE3 protocol (Version 13, dated May 13, 2014). However, the criterion was removed in subsequent versions (Version 15, amended on March 23, 2015) due to recommendations from the investigators and Data Safety Monitoring Board (DSMB) that the Nottingham score and its components define the level of risk and are sufficient to replace the Ki-67.

Pre-defined Study Endpoints

Primary Endpoint

The primary endpoint was the local recurrence rate (In-Breast Tumor Recurrence rate or IBTR rate) assessed at 5 years.

Local recurrence was pre-specified in the ICE3 protocol as evidence of invasive or in situ breast cancer in the ipsilateral breast or chest wall. Patients who developed clinical evidence of tumor recurrence in the remainder of the breast or chest wall were required to have a biopsy of the suspicious lesion to confirm the diagnosis. All biopsy-confirmed recurrences in the ipsilateral breast were considered in the analysis of the primary endpoint.

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, based on the NCCN Distress Thermometer patient survey
- Breast cosmetics satisfaction, based on subjects' and physicians' rating of cosmetic results on a 5-point scale (1-very dissatisfied to 5-very satisfied) at each follow up
- 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 (OS) 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

Safety Endpoints
The safety profile was determined by assessing the incidence of post-treatment complications and adverse events throughout the study period.

Key Statistical Analysis Methods
IceCure Medical estimated IBTR rate using the Kaplan-Meier (KM) method. The pre-defined success criterion for the primary endpoint was based on comparison to a 10% performance goal. The protocol specified that if the upper limit of the two-sided 95% confidence interval at the 5-year time point is less than 10%, the study will be considered successful. The performance goal was derived from a reference margin (5%) plus a reference rate (5%) drawn from a literature review conducted by IceCure Medical. Censoring methods and detailed methods for determining event time in the KM calculations were not pre-specified in the protocol.

Sample Size
For sample size determination, IceCure Medical assumed that the local recurrence rate for patients receiving the ProSense cryoablation system treatment would be equal to IceCure Medical's literature-derived rate of 5.0%. The protocol pre-specified enrollment of 150-200 subjects to ensure a sample size of 150 to allow estimation of the IBTR rate with ±5% level of accuracy. For a two-sided 95% exact Clopper-Pearson confidence interval, a binomial proportion whose true value is 5%, a sample size of 150 yields a half-width of at most 5% with a conditional probability of over 99%.

Study Procedures

Patients underwent imaging by mammography, ultrasound, and optional breast MRI for pre-registration to ensure eligibility. All fully eligible and registered patients were then treated with cryoablation therapy followed by 6 month and annual mammograms, and physical examinations for 5 years post-treatment. If the target lesion was only visible via ultrasound and not by mammogram, an MRI was required before the cryoablation procedure, and then at 6 months, 12 months, and annually thereafter for 5 years.

Each subject underwent a cryoablation treatment session. The cryoablation procedure was performed under ultrasound visualization by trained physicians. The cryogenic system was activated according to the ProSense cryoablation system User Manual. Default treatment times were a 9-minute first freeze followed by an 8-minute thaw, then ending with a 9-minute second freeze. However, since the ice ball growth varies from patient to patient (e.g., due to differences in tissue density) treatment times were controlled at the operator's discretion. Per the ICE3 protocol, treatment times were to be adjusted to target an ice ball width measurement >35 mm at the end of the first freeze (determined by adding 10 mm to each side of the largest tumor dimension), and an ice ball width measurement >40 mm at the end of the second freeze. In case of close tumor proximity to the skin, sterile saline was injected between the skin and the forming

ice ball, increasing the distance between the ice ball and dermis, thereby protecting the skin from thermal injury. A minimum of 5 mm distance between the ice ball and the dermal layer of skin was recommended to prevent injury.

All subjects in the ICE3 study were treated with two (2) freeze/thaw cycles. The average time of the first freeze was 8.5 ± 1.9 min (median 8.5 min, range 2.8-13.0 min). The average ice ball dimensions after the first freeze were: width 31.8 ± 4.0 mm (median 31.5 mm, range 23.3-47.7 mm) and length 44.7 ± 6.1 mm (median 45.0 mm, range 30.0-58.0 mm). The average time of the second freeze was 8.5 ± 2.1 min (median 8.2 min, range 4.0-13.8 min). The average and range of ice ball dimensions after the second freeze were: width 36.9 ± 5.1 mm (median 36.8 mm, range 24.5-61.0 mm) and length: 46.9 ± 6.8 mm (median 48.2 mm, range 36.0-65.5 mm). The margin between the ice ball front and the tumor edge was an average of 11.4 mm on each side of the tumor after the first freeze, and 13.9 mm after the second freeze. Saline injections were used in 133/194 procedures (68.5%). The average total procedure time was 24.8 ± 5.1 min (median 24.8 min, range 10.5-39.3 min) in the ICE3 study.

At the end of the procedure, the investigator documented baseline lesion sizes (as measured by ultrasound), procedure data, and ice ball measurements (also measured by ultrasound). In addition, the investigator evaluated and recorded any observed and reported adverse events. Endocrine therapy, chemotherapy, and/or radiation therapy as indicated by the stage of the disease and tumor biology, were provided at the discretion of the treating physician. All subjects were asked to return for follow-up visits at 6, 12, 24, 36, 48, and 60 months following the last treatment. The treating investigator performed a physical examination, evaluated and recorded imaging results and any adverse events, and documented physician satisfaction at each follow-up visit until 60 months from the procedure date.

Protocol Deviations

The number of protocol deviations by type and classification ('major' or 'minor') are summarized in **Table 3**. IceCure Medical reported a total of 448 protocol deviations for 157 subjects, of which 56 were categorized as major deviations. There were 45 deviations from the pre-specified inclusion/exclusion criteria for 44 patients.

Table 3. Summary of ICE3 study protocol deviations by type and classification.

Deviation Category	**Major**		**Minor**		**Total**	
	Events	Subj.	Events	Subj.	Events	Subj.
Missed Visit	0	0	20	16	20	16
Visit Out of Window	0	0	203	113	203	113
Violation of Inclusion/Exclusion Criteria	45	44	0	0	45	44
Follow Up Procedural Deviation	2	2	160	69	162	69
Informed Consent Deviations	2	2	2	2	4	4
Other (e.g., use of neoadjuvant hormone blockage, inadequate procedure time, incomplete treatment)	7	7	6	8	13	15

Subject Disposition and Baseline Characteristics

The trial screened 212 patients, 206 of which were treated with cryoablation using the ProSense cryoablation system. Of the 206 patients treated, 13 patients were lost to follow-up, 29 withdrew, and 21 died (one after 5 years). An additional 12 patients were excluded by the Data Safety Monitoring Board (DSMB) due to inclusion/exclusion criteria violations (N=9; violations included tumor size >1.5 cm, presence of multifocal disease and extensive intraductal component, and prior lumpectomy) or incomplete treatment (N=3; due to device malfunction or insufficient ice ball size); the participation of these 12 subjects was withdrawn after cryoablation treatment but prior to their completing the study. Thus, in total, 131 subjects completed the 60-month follow-up visit. See **Figure 3** for a flowchart of patient disposition.

The subject demographics and tumor characteristics of all 206 treated subjects are shown in **Table 4**. The mean age of the patients was 74.9 ± 6.9 years (range 55–94 years; median 74.5 years). The enrolled patient population consisted of females (100%), with luminal A (98%), ER positive (100%), PR positive (93%) breast cancer. Adjuvant treatment was provided following the procedure based on the physician's discretion; 78% (161 of 206) of subjects received adjuvant treatment. 178 subjects were treated by surgeons and 28 subjects were treated by radiologists in the ICE3 study.

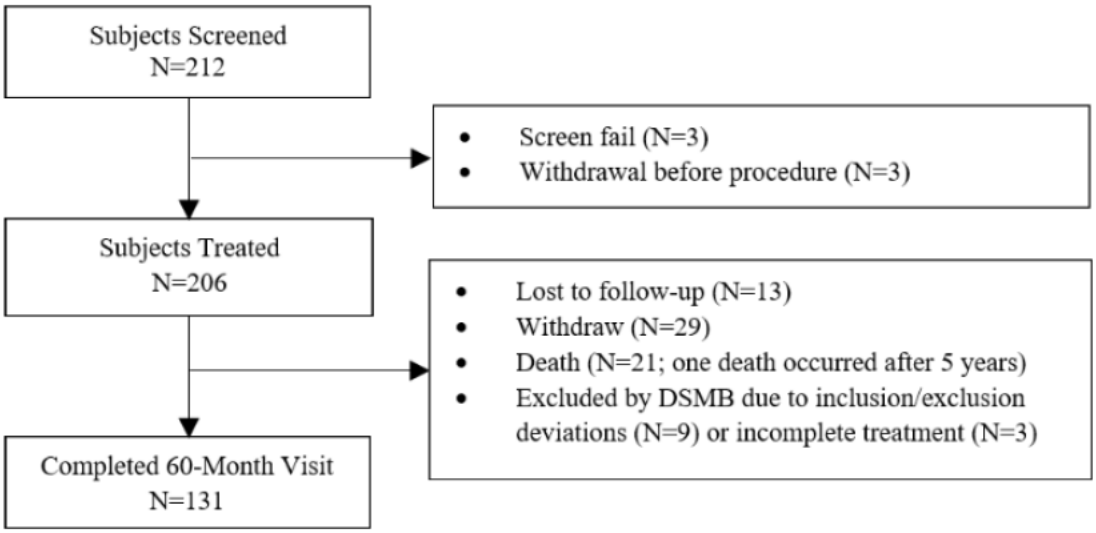


Figure 3. ICE3 trial patient disposition flowchart.

Table 4. Baseline demographics, tumor characteristics, adjuvant treatments, and treating physician type of all subjects treated with cryoablation using the ProSense cryoablation system in the ICE3 trial (N=206).

	N	% [1]
Sex		
Male	0	0%

Female	206	100%
Age		
55 to 60 years	4	2%
61 to 70 years	49	24%
71 to 80 years	105	51%
81 to 90 years	46	22%
91 to 94 years	2	1%
Ethnicity		
African American	15	7.5%
Asian	1	0.5%
Caucasian	169	84%
Hispanic	14	7%
Native American	2	1%
Unknown	5	-
Type of tumor		
Luminal A	200	98.5%
Luminal B	3	1.5%
Triple negative	0	0%
Basal like, HER2 Type	0	0%
Unknown	3	-
Estrogen Receptor (ER) status		
Positive	206	100%
Negative	0	0%
Progesterone Receptor (PR) status		
Positive	191	93%
Negative	15	7%
HER2 status		
Positive	0	0%
Negative	206	100%
Nottingham Grade [2]		
1	99	48%
2	107	52%
Ki-67 index		
Ki-67 <14%	99	71%
Ki-67 ≥14%	41	29%
Unknown [3]	66	-
Adjuvant Treatment		
Endocrine therapy only	132	66%
Radiation only	3	1.5%
Endocrine and radiation therapy	25	12%
Endocrine, radiation, and chemotherapy	1	0.5%
No adjuvant treatment or other	40	20%
Unknown	5	-

Treating physician type		
Surgeon	178	86%
Radiologist	28	14%

[1] Percentages are reported out of the total subjects with known information.
[2] FDA was unable to independently confirm the nuclear grade of 19 patients whose nuclear grade was not reported in study case reports. Of those with reported values, FDA identified 12 patients with nuclear grade 3 or 2-3. For some of these patients, the nuclear grade inclusion criterion was not required at the time of enrollment due to modifications to the study protocol.
[3] Ki-67 was initially defined as an inclusion criterion in the ICE3 trial protocol but was later removed. The Ki-67 is unknown for those patients enrolled after the inclusion criterion was removed from the protocol.

ICE3 Trial: Pivotal Study Results

Results Overview

The primary outcome of the ICE3 study was the 5-year IBTR rate (local recurrence rate). The IBTR outcome was assessed for all subjects enrolled and treated with cryoablation in the study (Full Analysis Set), and for a per protocol patient subset (Primary Analysis Set). To facilitate comparison of IBTR rate from the ICE3 study with standard of care IBTR rates reported in the literature, additional post-hoc subpopulation analyses of the ICE3 study results were performed. For a lower-risk ICE3 subpopulation of patients treated with adjuvant endocrine therapy (referred to herein as Lower-Risk Subpopulation), the IBTR rate was 2.3% (95% CI: 0.6-9.0%) based on two recurrences identified in this subpopulation (N=120). To compare this population's IBTR rate with standard of care (lumpectomy), a systematic literature review and meta-estimate performed by the sponsor and independently by FDA for a similar patient population showed a comparable IBTR rate of 2.82% (95% CI upper bound: 4.83%) and a point estimate range of 0 to 2.3%, respectively. A detailed discussion of the different analysis populations and their results, including secondary effectiveness outcomes and adverse events, is provided below.

Analysis populations

The study results were analyzed by IceCure Medical in the provided clinical study report based on a per protocol patient set only. FDA considers that all patients enrolled should be included in an intent-to-treat (ITT) analysis and the primary analysis should be based on this ITT population, because results from the ITT population accounts for deviations or non-compliance that might occur in practice during real-world use of the device. Accordingly, FDA performed an additional analysis of the ICE3 study results based on all subjects deemed eligible by the study investigators and treated with cryoablation in the ICE3 study. Patients with incomplete tumor ablation were included in the effectiveness and safety analyses by FDA.

- **Full Analysis Set (ITT)** (N=206): all subjects enrolled and treated with cryoablation in the study, including partial treatment.
- **Primary Analysis Set (per protocol)** (N=194): all subjects enrolled and treated in the study except 12 subjects excluded by the DSMB due to certain violations of the ICE3 protocol inclusion/exclusion criteria or incomplete cryoablation treatment.

The results of FDA's analysis for the Full Analysis Set are summarized in **Table 5**. The results of FDA's analysis for the Primary Analysis Set are summarized in **Table 6**.

Effectiveness Results – Primary endpoint: Local recurrence (IBTR)

The IBTR rate of the Full Analysis Set was 8.7% (95% CI: 5.2-14.5%) based on the cumulative incidence of local recurrences identified in 14 of the 206 treated subjects. Among the 14 subjects with local recurrence in the Full Analysis Set, the mean time to recurrence was 35.9 months and the median time to recurrence was 36.5 months. After recurrence, one (1) patient underwent lumpectomy but died due to metastatic breast cancer, one (1) patient underwent lumpectomy and died due to unknown causes, two (2) patients were treated with lumpectomy or partial mastectomy and survived for the duration of the study, two (2) patients declined further work-up and survived the full duration of the study, three (3) had partial mastectomy and withdrew early, and out of the five (5) patients who were withdrawn by the DSMB before study completion due to inclusion/exclusion deviations or partial cryoablation treatment; two (2) had lumpectomy, two (2) mastectomy, and one (1) had no information provided regarding treatment of recurrence. Two of the local recurrences were identified during the Month 60 visits, which occurred at month 61.87 and month 63.19. These subjects are included in the 5-year IBTR rate analysis given that their recurrence would have likely occurred within the 5-year study timeframe. Two other local recurrences categorized as IBTR by FDA due to evidence of recurrence were not categorized as such in IceCure Medical's clinical study report due to the patient declining biopsy to confirm imaging findings suspicious for recurrence in one case, and the investigator and/or DSMB categorizing the event as second primary breast cancer in the second case.

For the Primary Analysis Set, FDA identified nine (9) recurrence events, resulting in an IBTR cumulative incidence of 6.2% (95% CI: 3.2-11.7%). The mean time to recurrence in this analysis population was 47.2 months and the median time to recurrence was 51.6 months. As above, FDA's calculation includes two additional local recurrences that were not categorized as IBTR by IceCure Medical. Compared with the Full Analysis Set, the Primary Analysis Set (used by IceCure Medical in their clinical study report) excludes five recurrences that were identified in the 12 patients excluded by the DSMB (three subjects had tumors >1.5 cm, one subject had DCIS 40%, and one subject had undergone a prior lumpectomy and radiation and had multifocal tumor). These excluded subjects experienced recurrence earlier than average, between 7.5 and 28 months after treatment.

FDA also calculated the IBTR rate based on KM estimation methods for comparative purposes, as this was the statistical method pre-defined in the ICE3 protocol and used by IceCure Medical in their analysis; KM IBTR rates for the two analysis sets are shown in **Table 5** and **Table 6**. However, FDA used the Cumulative Incidence Function (CIF) IBTR rate in their assessment of benefit-risk because CIF accounts for the competing risk of death in the determination of IBTR rate. We also note that CIF is more commonly used in literature reports of IBTR rates, which were used as a comparator for the ICE3 results. FDA's KM calculation method also differs from the method used by IceCure Medical in their clinical study report with respect to censoring methods. Note, KM censoring methods were not pre-defined in the ICE3 protocol.

Effectiveness Results – Key secondary endpoints: DFS, OS, and Breast Cancer Survival

The key secondary endpoints related to 5-year oncological outcomes were DFS, OS, and Breast Cancer Survival. The study protocol definition of DFS included local recurrence, distant recurrence, second primary breast cancer, second primary non-breast cancer, and death due to any cause as events. Based on this definition, the KM estimate for DFS was 75.2% (95% CI:

67.7-81.2%) and 77.3% (95% CI: 70-83.1%) for the Full Analysis Set and the Primary Analysis Set, respectively. The KM estimate of OS was 88.6% (95% CI: 82.8-92.5%) and 88.4% (95% CI: 82.6-92.4%) for the Full Analysis Set and the Primary Analysis Set, respectively, based on 20 deaths within the 5-year analysis timeframe. Note, one additional death occurred outside of the 5-year timeframe and was not included in the calculation of the 5-year event rate. The KM estimate for the Breast Cancer Survival rate was 96.6% (95% CI: 92-98.6%) for both the Full Analysis Set and the Primary Analysis Set, respectively, based on two (2) deaths due to breast cancer and three (3) deaths due to unknown causes.

Table 5. Summary of the primary and secondary endpoint results for the ICE3 study based on Kaplan-Meier (KM) and Cumulative Incidence Function (CIF) calculations of the 5-year patient data for the Full Analysis Set of the ICE3 study (N=206), which represents the ITT analysis set used by FDA in the De Novo benefit-risk assessment.

ICE3 Full Analysis Set (N=206)				
5-year Outcome Measure	Event Type	# of events	FDA KM Rate (95% CI)[1]	FDA CIF Rate (95% CI)[1]
Primary Endpoint				
IBTR	Local recurrence[2]	14	9.5% (5.7-15.7%)	8.7% (5.2-14.5%)
Secondary Endpoints				
DFS	Local recurrence[2]	14	75.2% (67.7-81.2%)	-
	Distant recurrence	2		
	2nd primary BC	3		
	2nd primary non-BC	8		
	Death due to any cause	20		
	Total number of patients with events[3]	41		
OS	Death due to any cause	20	88.6% (82.8-92.5%)	-
Breast Cancer Survival	Death due to BC	2	96.6% (92-98.6%)	-
	Death unknown cause	3		

KM=Kaplan-Meier; CIF=Cumulative Incidence Function; IBTR=Ipsilateral Breast Tumor Recurrence; DFS=Disease-Free Survival; OS=Overall Survival; BC=Breast Cancer

[1]All CIs are nominal values and have no adjustment for multiplicity.
[2] Includes two patients categorized by FDA as having evidence of IBTR that were categorized by the investigator and/or DSMB as second primary breast cancer or suspicious for recurrence on imaging but not biopsy confirmed.
[3]Some patients experienced multiple events. DFS is calculated based on the patient-level rate.

Table 6. Summary of the primary and secondary endpoint results for the ICE3 study based on Kaplan-Meier (KM) and Cumulative Incidence Function (CIF) calculations of the 5-year patient data for the Primary Analysis Set of the ICE3 study (N=194), which represents the analysis set pre-defined in the ICE3 protocol as the primary analysis set and used in IceCure Medical's clinical study report.

ICE3 Primary Analysis Set (N=194)

5-year Outcome Measure	Event Type	# of events	KM Rate (95% CI)[1]	CIF Rate (95% CI)[1]
Primary Endpoint				
IBTR	Local recurrence[2]	9	6.8% (3.6-12.8%)	6.2% (3.2-11.7%)
Secondary Endpoints				
DFS	Local recurrence[2]	9	77.3% (70-83.1%)	-
	Distant recurrence	2		
	2nd primary BC	3		
	2nd primary non-BC	8		
	Death due to any cause	20		
	Total number of patients with events[3]	36		
OS	Death due to any cause	20	88.4% (82.6-92.4%)	-
Breast Cancer Survival	Death due to BC	2	96.6% (92-98.6%)	-
	Death unknown cause	3		

KM=Kaplan-Meier; CIF=Cumulative Incidence Function; IBTR=Ipsilateral Breast Tumor Recurrence; DFS=Disease-Free Survival; OS=Overall Survival; BC=Breast Cancer

[1] All CIs are nominal values and have no adjustment for multiplicity.

[2] Includes two patients categorized by FDA as having evidence of IBTR that were categorized by the investigator and/or DSMB as second primary breast cancer or (2) suspicious for recurrence on imaging but not biopsy confirmed.

[3] Some patients experienced multiple events. DFS is calculated based on the patient-level rate.

Safety Results

Procedure-related serious adverse events (SAEs) and adverse events (AEs) were assessed to determine the safety profile of the ProSense cryoablation system. A high-level summary is provided below.

Within the Primary Analysis Set (N=194), 133 SAEs were reported in 65 subjects (33.5%). One hundred and eighty (180) procedure-related events were reported by 93 subjects (47.9%). All cases of IBTR were considered as device-related serious adverse events because they cannot be definitively determined as unrelated to the device, which is intended for local treatment. As discussed above, fourteen (6.8%) IBTR were observed in the Full Analysis Set. **Table 7** shows the number of deaths, distant recurrences, IBTR, second primary breast cancer, and second primary non-breast cancer reported in the Full Analysis Set. Of the 14 subjects with local recurrence, one (1) patient died due to metastatic breast cancer.

Within the Primary Analysis Set (N=194), 140 patients (72.2%) reported 517 AEs. Ninety-three (93) subjects (47.9%) reported 180 procedure-related AEs, the most prevalent of which were bruising in 57 subjects (29.4%), pain in 36 subjects (18.6%), and localized edema in 35 subjects (18.0%). Validated pain scales, however, were not included in the study results. Six percent (6%) of patients in the Primary Analysis Set experienced complications during or shortly after the procedure and six percent (6%) experienced system malfunctions or device warning during the procedure.

Regarding oncology related SAEs only, Table 7 lists all SAEs in this category from the Full Analysis Set (N=206). The results show 14 IBTR cases (6.8%).

Table 7. Serious Adverse Events (SAEs) related to oncology results in the treated population of the ICE3 study (N=206).

SAEs in the Full Analysis Set (N=206)	
	n (%)
Deaths	21[2] (10.2%)
Deaths due to breast cancer	2 (1.0%)
Deaths due to unknown cause	3 (1.5%)
Distant recurrences	2 (1.0%)
IBTR[1]	14 (6.8%)
Second primary non-breast cancer	8 (3.9%)
Second primary breast cancer	3 (1.5%)

[1] Includes two patients categorized by FDA as having evidence of IBTR that were categorized in the clinical study report as second primary breast cancer or suspicious for recurrence on imaging but not biopsy confirmed.

[2] Includes 20 patient deaths recorded through the 60-month visit window and one patient death recorded at approximately 74 months.

The study also included secondary endpoints related to quality of life and cosmetic satisfaction. The study showed a 0.7-point improvement in distress at 6 months compared to baseline, based on the NCCN Distress Thermometer (scale of 1-10; 10=extreme distress, 0=no distress). Because the evaluation was at 6 months, the study did not assess distress or Quality of Life impacts related to recurrence events. Regarding breast cosmetic satisfaction, the study showed that of those responding to the survey, 98.8% of subjects (175 of 177) were 'satisfied' or 'very satisfied' with the cosmetic outcome of the procedure based on a 5-point scale (1-'very dissatisfied' to 5-'very satisfied') at the 6-month follow-up. Physicians rated being 'satisfied' or 'very satisfied' with the cosmetic outcome of the procedure in 98.8% of cases (174 of 176) at 6 months based on the same scale. At 5-years, 99.1% of patients (110 of 111) and 97.1% of physicians (99 of 102) were 'satisfied' or 'very satisfied' with the breast cosmetic outcome. Note, up to 15% of available patients did not complete the survey at a given follow-up visit. Due to the single-arm design of the study, a direct comparison of quality of life and cosmetic satisfaction with standard of care is not available.

Additional Post-Hoc Subpopulation Analysis

In addition to the full treated population of the ICE3 study and the primary analysis set, additional post-hoc analyses were conducted by FDA and the sponsor to facilitate benefit-risk assessment and comparison with similar, reproducible patient populations in the literature. The subpopulations were defined as follows:

- **Subpopulation with Adjuvant Endocrine Therapy (post-hoc)** (N=147): The sponsor analyzed a subpopulation of the primary analysis set defined post-hoc based on those subjects ≥60 years of age and receiving adjuvant endocrine therapy. Subjects in this subpopulation may have received adjuvant radiation therapy in addition to endocrine therapy

at the discretion of their provider. Patients receiving no adjuvant therapy after cryoablation or radiation therapy only were excluded.

- **Lower-Risk Subpopulation (post-hoc)** (N=120): FDA analyzed a lower-risk subpopulation of the primary analysis set defined post-hoc based on recurrence risk including patients ≥60 years of age with infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), unifocal tumor size ≤1.5 cm, ER-positive and/or PR-positive, HER2-negative, Nottingham grade 1-2 (specifically, nuclear and mitotic scores ≤2 per the ICE3 protocol inclusion/exclusion criteria), clinically negative lymph node (N0), and receiving adjuvant endocrine therapy. Subjects may or may not have also received adjuvant radiation therapy at the discretion of their provider. The primary difference between this lower-risk subpopulation and the primary analysis set is the exclusion of patients who did not receive endocrine therapy, patients with a nuclear score of 3, and patients with unreported Nottingham component scores.

The sponsor's analysis for the subpopulation with adjuvant endocrine therapy resulted in an IBTR rate of 3.1% (CIF; 95% CI: 1.0-7.2%) based on 4 recurrences identified in this subpopulation (N=147). The results of FDA's analysis for the Lower-risk Subpopulation are presented in **Table 8**. FDA's calculated IBTR rate was 2.3% (CIF; 95% CI: 0.6-9.0%) based on 2 recurrences identified in this subpopulation (N=120).

Table 8. Local recurrence (IBTR) rates for the post-hoc subpopulation analyses determined with CIF.

ICE3 Subpopulation with Adjuvant Endocrine Therapy (N=147)		
5-year Outcome Measure	# of events	CIF Rate (95% CI)
Local recurrence (IBTR)	4	3.1% (1.0-7.2%)
ICE3 Lower-Risk Subpopulation (N=120)		
5-year Outcome Measure	# of events	CIF Rate (95% CI)[1]
Local recurrence (IBTR)	2	2.3% (0.6-9.0%)

CIF=Cumulative Incidence Function; IBTR=Ipsilateral Breast Tumor Recurrence

[1]CIs are nominal values and have no adjustment for multiplicity.

Systematic Literature Review and Meta-Analysis

Sponsor literature review

The ICE3 clinical study was a single-arm study with no comparator arm. The performance goal for the primary endpoint (IBTR rate) was derived from a systematic literature review (SLR) and meta-analysis conducted by IceCure Medical. After the study was completed, at FDA's request, IceCure Medical updated the SLR to include articles published over the course of the study, covering articles published between 2003 and early 2024, for a post-hoc comparison. IceCure Medical's SLR identified 12 relevant articles of which 11 were included in a meta-estimate. IceCure Medical's SLR and meta-analysis resulted in an estimated 5-year IBTR rate of 3.52% (95% CI: 2.08-5.77%) for patients treated with lumpectomy and no radiation therapy. A

sensitivity analysis for patients treated with lumpectomy and endocrine therapy (and no radiation) resulted in a rate of 2.82% with an upper bound of the 95% CI of 4.83%.

While this SLR and meta-analysis provided valuable information about the outcomes of standard of care, the methodology had limitations, such as inclusion of patients who were at a higher risk for recurrence than the indicated population. Notably, the pre-specified SLR methods required that only 75% of patients in the individual articles align with the meta-analysis inclusion/exclusion criteria. As a result, some patients in the included study cohorts had higher risk factors for recurrence, such as lobular carcinoma, high tumor grade, multifocal tumors, and lymphovascular invasion; this could inflate the SLR comparator IBTR rate relative to the anticipated rate for patients enrolled in the ICE3 study. Additionally, IceCure Medical's SLR excluded patient cohorts receiving radiation therapy; approximately 15% of patients in the ICE3 study received radiation therapy. Radiation therapy has been shown to decrease IBTR rate in the intended patient population, so exclusion of these patients from the SLR can also inflate the IBTR rate relative to the anticipated rate for patients enrolled in the ICE3 study. Furthermore, the SLR was limited with respect to the search terms used to identify potentially relevant articles.

FDA literature review

FDA independently conducted an SLR and meta-analysis to inform the comparison of the ICE3 study outcomes with standard of care (surgical tumor resection via lumpectomy). The review focused on IBTR rate at 5 years as a primary outcome. FDA did not extract DFS information from the SLR due to inconsistencies in how DFS has been defined across breast cancer trials in the literature, with different events included as disease events (e.g., death due to any cause versus death due to breast cancer only). FDA's SLR was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Cochrane Handbook for Systematic Reviews of Interventions, with an exception for Study Selection and Data Extraction. For study selection, the inclusion criteria focused on a specific low-risk population.

FDA's approach targeted patients aged >50 years with specific breast cancer characteristics (tumor size ≤1.5-2 cm, Nottingham grade 1-2, ER+, PR+, HER2-, Ki-67<14%, clinically node-negative). We note that the patient age target in FDA's SLR of >50 years is younger than the post-hoc Lower-Risk Subpopulation analysis of ICE3 (≥60 years) and the average age of the ICE3 population (mean age 74.9 ± 6.9 years). We also note that Ki-67 was not used as an inclusion criterion in FDA's SLR, but where Ki-67 was reported to be >14%, these studies were excluded from the meta-analysis to facilitate an estimate more representative of low-risk patients. FDA's SLR also required that patients receive adjuvant endocrine therapy, per the proposed IFU of the ProSense cryoablation system. Note that approximately 20% of the ICE3 study population did not receive endocrine therapy; we compare the results of the SLR below to the subpopulations of the ICE3 study which received endocrine therapy per the IFU of the device in this submission. Also, as in the proposed IFU, there were no requirements in the SLR criteria related to the use of adjuvant radiotherapy. Approximately 15% of subjects in the ICE3 study received adjuvant radiation therapy.

FDA's independent SLR identified 25 articles relevant for qualitative assessment, of which only 5 met the most stringent criteria for inclusion into a meta-analysis. The IBTR values ranged from

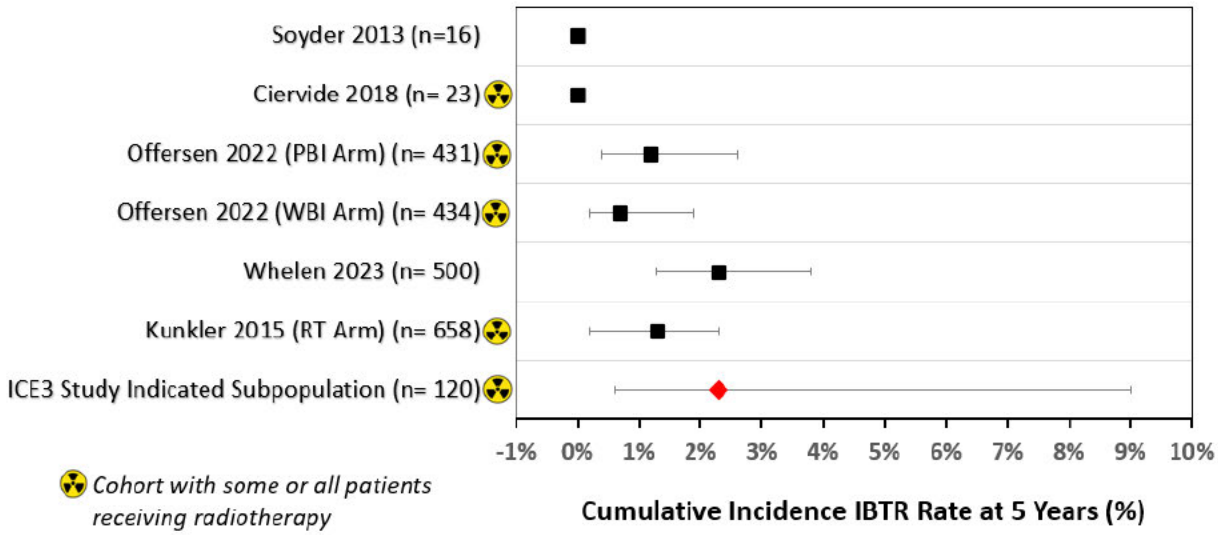
0% to 12% for different treatment arms and several studies had rates below 1% (**Table** 9). In a meta-analysis of the five studies meeting the most stringent inclusion/exclusion criteria comparable to the ICE3 intended subpopulation, point estimates for IBTR rate ranged from 0 to 2.3% (**Figure 4**). The overall number of studies included in the meta-estimate with extractable data matching the indicated population was low. We also note that two of the studies with fewer than 25 subjects had an IBTR rate of 0%.[1]

Table 9. Summary of FDA's SLR for early stage, low risk breast cancer patients treated with lumpectomy and adjuvant endocrine therapy.

Total Studies in the SLR	25	
Total SLR Sample Size	15,281 patients	Smallest: 12 patients (Liao 2011) Largest: 2,109 patients (Carleton 2021)
Treatment Modalities	Radiotherapy: 21 studies; Endocrine therapy: 23 studies; Both: 19 studies	
Study Designs	Randomized controlled trials: 8, Observational studies: 17	
Geographic Distribution	U.S.: 9 studies, UK: 4 studies, Italy: 3 studies, Other countries: 9 studies	
Follow-up Duration	≥ 10 years follow-up: 4 studies	
	≥ 5 years median follow-up: 15 studies	
Five-year IBTR Rates	20 studies reported an explicit 5-year IBTR rate: 5 studies reported 0% rates 9 studies reported rates of 1% or lower 12 studies reported rates of 2% or lower 15 studies reported rates of 3% or lower 17 studies reported rates of 4% or lower 19 studies reported rates of 5.9% or lower One study (Dhan 2020) reported rates of 12% (no adjuvant therapy), 1.5% (radiation therapy), and 4.2% (endocrine therapy)	

Figure 4. Five-year IBTR rate point estimates and confidence intervals for the five studies in FDA's independent SLR meta-analysis meeting the most stringent inclusion/exclusion criteria comparable to the ICE3 intended subpopulation, plotted against the IBTR rate observed in ICE3 for the intended subpopulation receiving adjuvant endocrine therapy (and radiation therapy at the physician's discretion).

[1] As discussed at the November 7, 2024, General and Plastic Surgery Devices Panel, FDA assessed the risk of bias associated with studies in the SLR, and these two studies have a higher risk of bias.



Comparison of ICE3 study results to the SLR and meta-analysis results

The results of IceCure Medical's and FDA's SLRs are compared to the ICE3 study results in **Table 10.**

Table 10. Five-year ipsilateral breast tumor recurrence (IBTR) rates from the ICE3 study compared to IBTR rate meta-analysis results from systematic literature reviews (SLRs) conducted independently by IceCure Medical and FDA for early stage, low risk breast cancer patients.

Analysis Population	Breast Cancer Treatment	5-year IBTR rate (95% CI)
ICE3 study results		
Full Analysis Set[1] (N=206)	• Cryoablation • Endocrine therapy and/or radiation therapy at the provider's discretion	8.7% (5.2-14.5%)
Primary Analysis Set[2] (N=194)	• Cryoablation • Endocrine therapy and/or radiation therapy at the provider's discretion	6.2% (3.2-11.7%)
Subpopulation with Adjuvant Endocrine Therapy[3] (N=147) (post-hoc)	• Cryoablation • Endocrine therapy • Radiation therapy at the provider's discretion	3.1% (1.0-7.2%)
Lower-Risk Subpopulation[4] (N=120) (post-hoc)	• Cryoablation • Endocrine therapy • Radiation therapy at the provider's discretion	2.3% (0.6-9.0%)
SLR and meta-analysis results		
IceCure Medical SLR (N=3,718)	• Lumpectomy • With & without endocrine therapy • No radiation therapy	3.52% (2.08-5.77%)

IceCure Medical SLR sensitivity analysis (N=3,490)	• Lumpectomy • Endocrine therapy • No radiation therapy	2.82% (upper bound 4.83%)
FDA SLR (N=2,062)	• Lumpectomy • Endocrine therapy • With & without radiation therapy	0%-2.3%

IBTR= Ipsilateral Breast Tumor Recurrence; CI= Confidence Interval; SLR= Systematic Literature Review
[1] All subjects enrolled and treated with cryoablation in the study (intent to treat; ITT)
[2] All subjects enrolled and treated in the study except 12 subjects with certain inclusion/exclusion criteria violations or incomplete cryoablation treatment (per protocol; PP)
[3] Subpopulation (post hoc) of the primary analysis set consisting of patients treated with adjuvant endocrine therapy.
[4] Lower-risk subpopulation (post hoc) of the primary analysis set consisting of patients treated with adjuvant endocrine therapy and Nottingham nuclear score ≤2.

Additional Subgroup Analysis

Given the small sample size of the ICE3 study relative to a low anticipated event rate for the primary endpoint (IBTR rate <10%), subgroup analysis by patient characteristics other than adjuvant treatment type (as presented above) was not practical to evaluate for potential association with safety and effectiveness outcomes. We provide here a summary of the number of recurrences identified in the ICE3 study by: sex, age, ethnicity, tumor characteristics, adjuvant treatment type, and treating physician type. However, the study was not statistically powered for any subgroup analyses, and calculation of the IBTR rate by these subgroups were not provided.

Table 11. Number of patients in the ICE3 study with evidence of ipsilateral breast tumor recurrence (IBTR) after ProSense cryoablation system treatment by patient demographic characteristics and other risk factors.

	Number of patients in the ICE3 study (out of 206)	**Number of patients with evidence of IBTR (out of 14)**
Sex		
Male	0	0
Female	206	14
Age		
<60	4	0
60-64	10	1
65-69	29	1
70-74	56	4
75-79	49	3
80-84	41	2
85-89	14	3
90+	3	0
Ethnicity		
African American	15	2
Asian	1	0
Caucasian	169	10

Hispanic	14	2
Native American	2	0
Unknown	5	0
Tumor size		
≤ 0.6 cm	40	4
0.61-0.99 cm	78	4
1.0-1.2 cm	55	2
1.21-1.5 cm	30	3
> 1.5 cm	3	1
Estrogen Receptor (ER) status		
Positive	206	14
Negative	0	0
Progesterone Receptor (PR) status		
Positive	191	12
Negative	15	2
Nottingham Grade		
1	99	1
2	107	13
Ki-67 index		
Ki-67 <14%	99	7
Ki-67 ≥14%	41	4
Unknown	66	3
Adjuvant Treatment		
Endocrine therapy only	132	7
Radiation only	3	0
Endocrine and radiation therapy	25	0
Endocrine, radiation, and chemotherapy	1	0
No adjuvant treatment or other	40	7
Unknown	5	0
Treating physician type		
Surgeon	178	13
Radiologist	28	1

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

PANEL MEETING RECOMMENDATION AND POST-PANEL ACTIONS

Panel Meeting Recommendation

At an advisory meeting held on November 7, 2024, the General and Plastic Surgery Devices Panel voted 9 Yes; 5 No; 0 Abstentions that the benefits of the ProSense cryoablation system outweigh the risks for the Indications for Use as originally proposed by IceCure in the De Novo submission.

The panel members who voted "no" expressed concerns about the intended patient population criteria and the degree of uncertainty in the risk assessment. They emphasized the need for more clearly defining the intended patient population, particularly regarding the age range of patients and the criteria for “low-risk” breast cancer. They also emphasized the need for more controlled data to accurately evaluate long-term risks, such as recurrence rates. There was also a call for additional safeguards, such as patient information about the potential risks and benefits, including the uncertainties regarding recurrence rates, and post-market surveillance, especially for younger patients.

The panel members who voted "yes" indicated that the ProSense cryoablation system demonstrated effectiveness comparable to standard of care in terms of IBTR rate, as reported in existing literature, or otherwise found the effectiveness acceptable considering other probable benefits of the device and different patient preferences. These members emphasized the likely quality-of-life benefits of surgery avoidance for certain patients, particularly those with limited access to care. They acknowledged that surgical options remain available if recurrence occurs and viewed the device as a safe and effective option for appropriately selected low-risk patients when combined with proper informed consent and patient monitoring. Some panel members who voted yes stipulated that the indicated age should be further limited, and some recommended post-market surveillance to address uncertainty.

Information from this advisory meeting can be found on FDA’s website at the following link: November 7, 2024: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee Meeting Announcement - 11/07/2024 | FDA (https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-7-2024-general-and-plastic-surgery-devices-panel-medical-devices-advisory-committee-meeting).

FDA’s Post-Panel Actions

Although the overall panel vote at the November 7, 2024 panel meeting was favorable, FDA worked interactively with the sponsor to implement risk mitigations suggested by the panel members, including: revisions to the indications for use, most notably to increase the age of the intended patient population to patients ≥70 years of age; development of patient labeling to inform patients of the benefits, risks, and uncertainties associated with the device; and development of a robust post-market study plan to collect additional information to reduce uncertainty regarding the oncological outcomes of patients within the intended use population.

POSTMARKET SURVEILLANCE

In order to satisfy special control (1) below, FDA has determined that IceCure Medical must collect and report post-market surveillance data acquired under anticipated conditions of use to demonstrate that the device performs as intended when used to treat the intended patient population. Specifically, the sponsor must conduct post-market clinical validation performance testing of the ProSense cryoablation system in patients to assess long-term tumor recurrence and other serious adverse events.

FDA expects that the postmarket study will enroll 400 patients at 30 sites to further characterize the ipsilateral breast tumor recurrence (IBTR) rate following cryoablation without resection for the treatment of low-risk, early-stage breast cancer in the indication population. The primary endpoint will be the percentage of patients who develop IBTR up to 5 years after cryoablation. IBTR will be defined as recurrent invasive or in situ cancer confirmed histologically in the ipsilateral breast and measured from the time of treatment to the time of documented ipsilateral recurrence. Histology showing a different molecular signature than the primary tumor treated with cryoablation will be defined as a second primary tumor (not IBTR). Time to recurrence and any subsequent ipsilateral breast surgeries (e.g., lumpectomy, mastectomy) performed for the treatment of residual or recurrent disease must be documented. The study is also expected to observe disease-free survival and overall survival rates.

LABELING

Device labeling includes the product labels on the device, instructions for use for providers, and patient labeling. The provider labeling includes a description of the device components and thermal outputs, device technical parameters, recommended training for safe use of the device, instructions for use of the device, and electromagnetic compatibility information. The document also states the shelf life for any sterile components as well as the necessary measures to properly dispose of any single use items and clean the reusable components of the device. The document also contains relevant findings from the ICE3 pivotal clinical study, including device treatment parameters and procedures, characteristics of the patient population, and treatment outcomes. The patient labeling includes a description of the intended patient population characteristics, treatment outcomes observed in clinical performance testing, and warnings regarding uncertainty or limitations in the clinical data. Both provider and patient labeling documents contain a statement that postmarket surveillance data is being collected.

Labeling also includes the following statements:

- The sale, distribution, and use of ProSense cryoablation system are restricted to prescription use in accordance with 21 CFR 801.109.
- Breast cancer treatment outcomes including recurrence rates, disease-free survival, and overall survival after use of this device are unknown beyond 5 years.
- ProSense's safety and effectiveness for breast cancer treatment were evaluated in a single-arm trial with 5 years follow up. Breast cancer treatment outcomes have not been studied in direct comparison to surgical excision (e.g., lumpectomy).
- Unlike surgical resection (e.g., lumpectomy) where there is a specimen for pathology to confirm whether the tumor was completely removed, cryoablation relies on imaging to determine where the tumor is located and if it was destroyed. However, the exact

boundaries may not be visible on imaging which can result in incomplete destruction of the tumor.

- The recurrence rate is being further evaluated in a larger patient population through an ongoing post-market study.
- ProSense cryoablation system is not intended as a treatment for recurrent breast cancer.
- ProSense cryoablation system is not intended for patients in whom neo-adjuvant chemotherapy and/or biological therapy or other targeted neo-therapies apart from endocrine therapy are indicated.
- ProSense cryoablation system is not intended as a treatment for breast cancers with inflammatory features.
- Only patients with adequate breast size can undergo safe breast cancer treatment with ProSense cryoablation system.
- Practices of cryoablation for women with breast implants have not been established. For patients with breast implants, you must document that adequate distance exists between the lesion and the implant to ensure that the ablated lesion will not contact or jeopardize the implant, and there is enough space to create the required margins.

Labeling will be updated in accordance with data collected via postmarket surveillance to provide updated clinical performance data and effectiveness data of the device.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a cryoablation device for local treatment of low-risk breast cancer and the measures necessary to mitigate these risks.

Risks to Health	**Mitigation Measures**
Incomplete tumor ablation resulting in the need for additional treatment(s) and/or tumor recurrence	Clinical performance testing Postmarket surveillance Non-clinical performance testing Software verification, validation, and hazard analysis Labeling
Electrical, thermal, or mechanical injury	Clinical performance testing Non-clinical performance testing Software verification, validation, and hazard analysis Electrical, mechanical, and thermal safety testing Electromagnetic compatibility testing Labeling
Infection and cross-contamination	Sterilization validation Shelf life testing Labeling
Adverse tissue reaction	Biocompatibility evaluation

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the cryoablation device for local treatment of low-risk breast cancer is subject to the following special controls:

(1) Data obtained from premarket clinical performance testing and postmarket surveillance conducted per a protocol approved by FDA and acquired under anticipated conditions of use must demonstrate that the device performs as intended in the intended patient population, unless FDA determines based on the totality of the information provided for premarket review that data from postmarket surveillance is not required. Premarket and postmarket clinical performance testing must demonstrate the 5-year ipsilateral breast tumor recurrence rate or other clinically justified endpoint for defining local treatment of breast cancer (e.g., histological clearance rate compared to a clinical comparator with known ipsilateral breast tumor recurrence rate), based on prespecified cryoablation device design and treatment parameters (e.g., imaging protocol, number of freeze/thaw cycles, treatment margin around the tumor, and target ice ball size). A discussion of how the intended and studied patient populations constitute a low-risk breast cancer population must also be provided.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including the following:
   (i) Performance testing must demonstrate that the device meets cryogen pressure and flow rate specifications with the intended cryogen type;
   (ii) Performance testing must characterize the dimensions of the active part of the applicator and demonstrate that the cryoprobe meets temperature specifications for freezing and thawing; and
   (iii) Performance testing must demonstrate that the device meets freezing performance specifications under the anticipated load in a representative test medium.

(3) Software verification, validation, and hazard analysis must be performed.

(4) Performance testing must demonstrate the electrical safety, mechanical safety, thermal safety, and electromagnetic compatibility of any electrical components of the device.

(5) Performance data must demonstrate the sterility of all patient-contacting device components.

(6) Performance data must support the shelf life of the device components provided sterile by demonstrating continued sterility and package integrity over the labeled shelf life.

(7) Performance data must demonstrate that all patient-contacting components of the device are biocompatible.

(8) Labeling must include:
   (i) Recommended training for safe use of the device;

(ii) Instructions for determining and achieving the appropriate ice ball size relative to the intended ablation volume;
(iii) A summary of clinical performance testing, including device treatment parameters and procedures, characteristics of the patient population, and treatment outcomes (e.g., recurrence rate, disease-free or event-free survival, overall survival, histological clearance rate, adverse events, patient-reported outcomes);
(iv) Warnings regarding uncertainty or limitations in the clinical data, including:
(A) The duration of oncological outcomes that have been evaluated; and
(B) A statement that oncological outcomes have not been studied in direct comparison to surgical tumor resection, unless such data are available, in which case comparison data must be included; and
(v) When postmarket surveillance is required per paragraph (1) of this section, a description of the postmarket surveillance purpose, and a summary of all postmarket surveillance data collected, including updated labeling to accurately reflect outcomes observed in postmarket surveillance.

(9) Patient labeling must include:
(i) A description of the intended patient population characteristics;
(ii) Treatment outcomes observed in clinical performance testing;
(iii) Warnings regarding uncertainty or limitations in the clinical data, including the duration of oncological outcomes that have been evaluated;
(iv) Warning regarding the limitations of using imaging to confirm the completeness of tumor destruction after cryoablation; and
(v) When postmarket surveillance is required per paragraph (1) of this section, a description of the postmarket surveillance purpose, and a summary of all postmarket surveillance data collected, including updated labeling to accurately reflect outcomes observed in postmarket surveillance.

BENEFIT-RISK DETERMINATION

Risks and Other Factors

FDA considered the probable risks of the ProSense cryoablation system when used in lieu of standard of care lumpectomy for the intended patient population as follows:

- *Incomplete tumor ablation requiring additional treatment(s) or resulting in tumor recurrence* When tumors are surgically excised, per current standard of care practices, surgical specimens are evaluated by histopathology to inform the need for retreatment. After cryoablation, there is no surgical specimen to assess with histopathology, so imaging is used to assess tumor extent before treatment and to monitor the completeness of destruction during and after cryoablation treatment. Unlike histopathology, which can detect microscopic residual disease, commonly used imaging modalities such as ultrasound and mammography tend to underestimate the tumor size and cannot completely detect residual disease. MRI is a more accurate imaging tool that could be used for preliminary assessment of tumor size, informing patient selection, and active monitoring for recurrence, but is also limited in its ability to detect residual disease immediately after treatment. Additionally, the pathology

specimen after surgical excision is often informative for patient management decisions in the case that the larger surgical specimen provides more information about the disease than the initial core biopsy used for diagnosis, such as information about molecular receptors, genetic signature, and Ki-67 index. This information is not available after cryoablation.

While foundational studies using an 'ablate and resect' design have shown relatively high rates of histological clearance for cryoablation of small, unifocal tumors, it is difficult to identify which patients have incomplete cryoablation in practice, as the treated area will not be subsequently excised. The ICE3 study provided information regarding the recurrence rate after tumors have been destroyed using cryoablation and are not surgically excised ('ablate and follow' design). The IBTR rate demonstrated in the single-arm ICE3 study appears to be comparable to that of patients receiving the current standard of care lumpectomy procedure, based on the available data from SLR and meta-analysis for lumpectomy. However, without a control arm of the ICE3 study with a similar distribution of patient characteristics, it is difficult to compare the results to standard of care treatment outcomes. In a subpopulation of the ICE3 study with particularly low risk breast cancer (as assessed by patient age, tumor size, tumor type, hormone receptor status, histological grade, lymph node status, and Ki-67 proliferation index) and receiving adjuvant hormone therapy, the IBTR rate after cryoablation was closer to standard of care rates reported in the literature for a similar population receiving lumpectomy and hormone therapy, although uncertainty around the IBTR rate estimates remains given the differences between the ICE3 and SLR patient cohorts.

In the case of device malfunction and incomplete treatment clearly detected with imaging, patients may undergo a salvage lumpectomy procedure to achieve adequate local breast cancer treatment. However, in the event of undetected incomplete treatment, the patient is at risk of recurrence. The significance of local recurrence is notable. Treatment for breast cancer recurrence is multi-modal including: surgery to resect the recurrence, which may involve partial or total mastectomy, systemic therapy (typically chemotherapy); and/or radiation therapy. Patients diagnosed with recurrence may experience a decline in functional status and quality of life. Additionally, the risk of developing subsequent distant metastases and death may be greater for women who experience a local recurrence than for women without a local recurrence. The ICE3 study did not provide information on patient outcomes beyond 5 years, which is insufficient to assess the long-term risks of treatment in this patient population, including effects on overall survival.

- *Procedure-related risks*
  Besides IBTR, the most prevalent procedure-related AEs were localized edema, bruising, and pain, which resolved without residual effects.

Benefits

FDA considered the probable benefits of the ProSense cryoablation system when used in lieu of standard of care lumpectomy for the intended patient population as follows:

- *Invasive surgery avoidance*
  The ProSense cryoablation system offers a minimally invasive method of destroying localized breast tumors ≤1.5 cm and can be performed under local anesthesia. If patients

were to undergo treatment with the ProSense cryoablation system, they would forego or delay the current standard of care lumpectomy surgical procedure for the treatment of their breast cancer. While lumpectomy of 1.5 cm tumors can be conducted under local anesthesia, and is considered to be a low-risk procedure, complications can occur, including seroma, infection, incisional pain, and/or numbness. Patients may also have impacts on the cosmetic appearance of their breast due to the combined effects of lumpectomy and radiation where used. The ICE3 study collected data indicated satisfaction with the cosmetic results in those patients providing a rating during follow-up visits. Additionally, cryoablation can be performed by both surgeons and radiologists; expansion of the treating physician type for this disease to include radiologists may be beneficial for patients who have limited access to cancer care.

- *Breast cancer treatment outcomes*
  A subpopulation of the overall ICE3 study population aligned with the authorized indications for use (low-risk patients receiving adjuvant endocrine therapy) had an IBTR rate of 2.3% (95% CI: 0.6-9.0%). The probable benefit over standard of care cannot be directly determined due to the single-arm design of the ICE3 study. However, based on FDA's SLR, standard of care IBTR rates for early stage, low risk breast cancer patients receiving lumpectomy and adjuvant endocrine therapy ranged from 0 to 2.3%. Thus, cryoablation appears to have a local treatment effect comparable to standard of care in low-risk patients, as assessed by IBTR rate.

<u>Uncertainty</u>
There is uncertainty in the benefit-risk assessment due to the following:

- *Unknown complete ablation rate*
  Foundational studies using an 'ablate and resect' design to determine the complete ablation rate after cryoablation were not conducted with the ProSense cryoablation system. Histological clearance could not be assessed from the 'ablate and follow' ICE3 pivotal study.

- *Uncertainty in the IBTR rate*
  The two-sided 95% confidence interval for the IBTR rate spanned a nearly 10% range, due to a limited sample size, high missing data rate at the 5-year endpoint, and other factors. The sample size (N=206) was small relative to the low anticipated recurrence rate for the intended patient population. Additionally, the ICE3 study did not control for all key risk factors, such as adjuvant therapy, which can have a significant impact on recurrence rate. A post-hoc analysis of the intended subpopulation, which received adjuvant endocrine therapy, had an even smaller sample size (N=120). Due to the small sample size, data is also lacking for subgroups of patients with certain risk factors for recurrence, such as Hispanic and African American patients, and only a limited number of subjects were treated by radiologists, who represent a new treating physician type for breast cancer. A total of 46 out of 206 subjects did not have data available at the 60-month study endpoint, which represents a missing data rate of over 20%. This includes 26 subjects without IBTR who withdrew, 7 subjects excluded prior to a recurrence event by the DSMB, and 13 subjects lost to follow-up during the 5-year study. Protocol revisions and deviations during the study add further uncertainty in the

reproducibility of the ICE3 IBTR rate results. To partially mitigate this uncertainty, postmarket surveillance is being required to further evaluate the 5-year IBTR rate in a larger sample size of patients.

- *Uncertainty in long-term outcomes and effects on survival*
  The risk of IBTR and survival outcomes beyond 5 years is unknown. In the low-risk breast cancer population studied, survival effects are not readily assessed within a 5-year timeframe.

- *Lack of direct comparator*
  As the ICE3 study was a single arm trial, there is no data available that directly compares the treatment outcomes, adverse events, or cosmetic outcomes between lumpectomy and ProSense cryoablation. Imperfect matching between patient characteristics in the ICE3 study population and literature for standard of care creates uncertainty in the comparison. FDA identified only five literature studies with six patient cohorts closely matching the intended patient population, and two of these studies had fewer than 25 patients. The SLR is further limited in its ability to align the distribution of patient characteristics within the analysis to that of the ICE3 study population and subpopulation(s). For example, adjuvant treatments like endocrine therapy and radiation therapy have a significant impact on treatment outcomes, yet the ICE3 study did not have enrollment criteria related to these treatments. In FDA's SLR and meta-analysis, four of the six cohorts received radiation therapy, whereas only about 15% of the ICE3 study population received radiation therapy. Age is another key risk factor that may not share similar distributions between the ICE3 study population and the literature study populations used to derive a comparator.

Patient Perspectives

As a supportive secondary endpoint, patient cosmetic satisfaction results (based on a 5-point scale; 1-very dissatisfied to 5-very satisfied) were reported in the ICE3 pivotal study. Among all the patients who responded in the Primary Analysis Population, 28% were satisfied and 70% were very satisfied at 6 months through 5 years time points. However, 15% of subjects did not complete the cosmetic satisfaction survey at a given visit. In addition, the single-arm design of the study does not allow direct comparison with standard of care cosmetic outcomes and satisfaction.

During the Advisory Panel meeting, both panelists and patients providing testimony in the open public hearing emphasizing the importance of offering patients choices, as individual preferences regarding surgery avoidance and certainty of treatment outcomes vary. Some patients may prioritize avoiding surgery even if it means accepting a higher risk of recurrence, while others might prefer the certainty of traditional surgery despite its associated risks and recovery time. It was noted that this difference in patient preference is currently observed in decisions regarding the use of radiation therapy in the indicated patient population. Several panelists noted that surgery avoidance is highly appealing to patients, particularly in terms of the convenience and reduced downtime associated with the ProSense procedure, and that this may be especially relevant for patients in rural areas who have limited access to cancer care. However, some panelists noted the trade-off between avoiding surgery and the risk of needing additional imaging studies, such as MRIs, which could lead to further biopsies and interventions. Some panelists felt there was adequate information available for patients to make an informed decision, while other panelists raised concerns that the ICE3 study does not clearly elucidate the risk of recurrence.

Patient labeling is required for the ProSense cryoablation system to assist patients in making informed decisions about treatment options and their care.

Benefit/Risk Conclusion

In conclusion, given the available data provided premarket, coupled with a postmarket surveillance plan to collect additional IBTR rate data following breast cancer treatment using the ProSense cryoablation system, the information supports that the probable benefits outweigh the probable risks for the device for the following indication statement:

> ProSense cryoablation system is indicated for the local treatment of breast cancer in patients ≥70 years of age with biologically low-risk tumors ≤1.5 cm in size and treated with adjuvant endocrine therapy, including patients not suitable for surgery for breast cancer treatment.
>
> Biologically low-risk breast cancer is defined as unifocal tumor, size ≤1.5 cm, ER-positive, PR-positive, HER2-negative, Ki-67<15% and/or genomic testing indicative of low-risk breast cancer, infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).

The device provides probable benefits, and the probable risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the ProSense cryoablation system is granted, and the device is classified as follows:

> Product Code: QXW
> Device Type: Cryoablation device for local treatment of low-risk breast cancer
> Regulation Number: 21 CFR 878.4355
> Class: II