FDA Executive Summary

General and Plastic Surgery Devices Panel Meeting

November 7, 2024

DEN(b) (4)

De Novo request for

IceCure Medical, Ltd.'s ProSense™ Cryoablation System

Based on Data from the ICE3 Study

Table of Contents

List of Appendices

List of Abbreviations

AJCC	American Joint Committee on Cancer
BCS	Breast Conserving Surgery (lumpectomy)
CIF	Cumulative Incidence Function
CRF	Case Report Form
DCIS	Ductal Carcinoma in situ
DDFS	Distant-Disease-Free Survival
DFS	Disease-Free Survival
DSMB	Data Safety Monitoring Board
ER	Estrogen Receptor
EIC	Extensive Intraductal Component
HER2	Human Epidermal Growth Factor Receptor 2
IDE	Investigational Device Exemption
IBTR	Ipsilateral Breast Tumor Recurrence
KM	Kaplan-Meier
LVI	Lymphovascular Invasion
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PR	Progesterone Receptor
RT	Radiotherapy
SEER	Surveillance, Epidemiology, and End-Results
RT	Radiation Therapy or Radiotherapy

List of Tables

Tables in the Appendices

List of Figures

Figures in the Appendices

1 Introduction

This is the Executive Summary for a panel meeting discussing the De Novo submission (DEN(b) (4)) submitted by IceCure Medical, Ltd. ("IceCure Medical") for the ProSense™ Cryoablation System (hereafter referred to as the "ProSense System").

IceCure Medical is requesting their De Novo submission be granted in order to market the ProSense System for use in patients with early stage, low-risk breast cancer as an alternative to breast conserving surgery, also known as lumpectomy, which is the current standard of care surgical treatment. IceCure Medical proposes indications for use "*in the treatment of patients with early stage, low risk breast cancer for the treatment of breast cancer with adjuvant endocrine therapy*." Within this context, an "early stage, low risk" population is defined by IceCure Medical in the indications for use statement as patients ≥60 years of age with unifocal tumor size ≤1.5 cm, Estrogen Receptor positive, Progesterone Receptor positive or negative, Human Epidermal Growth Factor Receptor 2 negative, histological grade 1-2 infiltrating (also referred to as invasive) ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).

Clinical data from background literature and the ICE3 pivotal study are used to inform the probable benefit and risk of the device for the proposed indications for use. The background literature reports on the success of other commercial cryoablation devices to completely destroy tumors of different sizes (up to 2 cm) based on '*ablate and resect'* study designs, in which tissue was treated with cryoablation and then surgically removed for histological evaluation. The ICE3 pivotal study was a prospective, multi-center (19 U.S. sites), single-arm trial in which 206 subjects with early stage, biologically low-risk breast cancer, were treated by the ProSense System and then followed to evaluate long-term outcomes ('*ablate and follow'* design*).* The primary endpoint in the ICE3 study was Ipsilateral Breast Tumor Recurrence (IBTR) rate at 60 months.

This Advisory Committee meeting is being held for the Panel to discuss and make recommendations regarding the probable benefits and risks of the ProSense System for the proposed indications for use based on the clinical data submitted in DEN . This Executive Summary includes a brief review of the current standard of care for early stage, low-risk breast cancer, relevant regulatory context, a description of the ProSense System, a discussion of the clinical data provided in the De Novo submission, and a summary of the systematic literature review conducted to assess the outcomes of standard of care.

2 Clinical Context

2.1 Breast Cancer Epidemiology, Diagnosis, and Staging

Breast cancer is the most commonly diagnosed cancer among U.S. women excluding nonmelanoma skin cancer. In the U.S., 1 in 8 women will develop breast cancer during their lifetime.[1-4] Infiltrating, also known as invasive, ductal carcinoma is the most common histological type of breast cancer, representing 70-80%.[5]

Mammography is typically used for screening and detection of breast cancer. However, in certain cases, breast ultrasound or magnetic resonance imaging (MRI) with contrast may be used. Breast ultrasound is similar in sensitivity to mammography and can be used to obtain an image-guided

biopsy, while MRI is the most sensitive breast imaging modality.[6] Definitive diagnosis of breast cancer is made by biopsy, typically via an image-guided core needle sampling of the tumor. Pathological analysis of biopsied tissue is used to determine whether breast cancer cells are present, and to evaluate the biopsied tissue using molecular assessments, such as tumor receptor status (e.g., estrogen receptors, progesterone receptors, and Human Epidermal Growth Factor Receptors).

The pathology findings from biopsied tissue, together with anatomic characteristics of the cancer, are used to determine staging. **Table 1** details the range of anatomical and pathologic criteria for breast cancer staging. The staging system most often used for breast cancer is the American Joint Committee on Cancer (AJCC) TNM staging system. The AJCC Staging system was initially a solely anatomic method to stage breast cancer, but advancements in tumor biology and prognostic biological markers, such as hormone receptors and the Human Epidermal Growth Factor Receptor 2 (HER2), have allowed clinicians to understand why similarly staged patients have significantly different outcomes. Accordingly, the most recent AJCC TNM staging system, effective January 2018, incorporates both clinical and pathologic elements to determine staging. Although not incorporated in the current version of the AJCC staging system, the St. Gallen International Consensus Guidelines further recommend assessing the cellular proliferation index by Ki-67. This index, together with other factors described above, is used to classify breast cancer into Luminal sub-types.[7-9]

Table 1. Summary of the anatomical and pathologic criteria used for breast cancer staging.

Anatomic and pathologic criteria for breast cancer staging		
Anatomic factors *Approximately 66% of breast cancer cases are diagnosed at a localized stage.[3]*	T: Extent (size) of the tumor	T1 tumors are ≤2 cm in the greatest diameter
	N: Spread to nearby lymph nodes	N0 cancer has not spread to lymph nodes
	M: Spread (metastasis) to distant sites	M0 cancer has not spread to distant organs
Nottingham Grade Pathology assessment of cellular characteristics	Glandular/tubular differentiation (Score 1-3)	The composite score of all three characteristics determines Grade as follows: Grade 1: total score of 3, 4, or 5 Grade 2: total score of 6 or 7 Grade 3: total score of 8 or 9
	Nuclear pleomorphism (Score 1-3)	
	Mitotic rate (Score 1-3)	
Presence of hormone receptor proteins Pathology assessment of cellular composition *HR positive, HER2 negative represents 70% of breast cancers.[1, 10]*	Estrogen Receptor (ER)	ER positive cancers have ER proteins
	Progesterone Receptor (PR)	PR positive cancers have PR proteins
	Hormone Receptor (HR)	HR positive cancers have receptors for estrogen, progesterone, or both hormones
	Human Epidermal Growth Factor Receptor 2 (HER2)	HER2 positive breast cancers have high HER2 protein expression
Ki-67 cellular proliferation index	Ki-67 >14%	Many cells are dividing quickly and cancer is likely to grow and spread

Pathology assessment of the percentage of cells positive for Ki-67	Ki-67 <14%	Tumors are considered "low proliferation" with fewer cells dividing quickly.
Luminal sub-types AJCC & Ki-67 are used to classify breast cancer into Luminal sub-types *Luminal A is the most common subtype (>50%), characterized by low grade and the best prognosis.*	Luminal A	ER positive PR positive HER2 negative Ki-67 < 14%
	Luminal B	ER positive PR negative (possible) HER2 negative or positive Ki-67 >20%

2.2 Breast Cancer Treatment

Since the 1960s, large, cooperative group, randomized trials have established surgery combined with radiation and systemic therapy as the current standard of care for breast cancer treatment.[10-15]

Breast Conserving Surgery (BCS), also known as lumpectomy, with negative surgical margins is the standard of care surgical treatment for most patients with early stage (e.g., T1 N0) invasive breast cancer.[15-17] The goals of BCS are to obtain tumor-free resection margins, while maximally maintaining the cosmetic appearance of the remaining breast. The phrase "*No tumor on ink*", interpreted to mean that there are no cancerous cells touching the edge of the pathology specimen, has been adopted as the definition of negative margins and as adequate local control for invasive breast cancer.[18, 19] Lumpectomy of small tumors can be conducted under local anesthesia and is generally considered to be a low-risk procedure; however, complications can occur, including seroma, infection, incisional pain, and/or numbness.

Adjuvant hormone therapy, including selective estrogen receptor modulators (e.g., tamoxifen) or aromatase inhibitors (e.g., exemestane, letrozole) are indicated in hormone receptor positive breast cancers.[16] Hormone therapy – also referred to as endocrine therapy – reduces the risk of breast cancer recurrence, second primary breast cancer, and mortality, and patients typically receive hormone therapy for between five and ten years.[18, 20-25] Despite reducing the risks associated with breast cancer, hormone therapy is not without its own risks. For example, tamoxifen is associated with an increased risk of thromboembolism, hot flashes, cataracts, ischemic cerebrovascular events, venous thromboembolic events (including deep-vein thromboses), vaginal bleeding and endometrial cancer. Additionally, aromatase inhibitors are associated with increased risk of bone loss and fractures.[22, 26]

Adjuvant radiation therapy (also referred to as radiotherapy) is also commonly used following lumpectomy. In 2002, the NSABP B-21 study demonstrated that the addition of radiotherapy to lumpectomy and tamoxifen significantly reduced the risk of local recurrence after lumpectomy in women with node-negative (N0) invasive breast cancers up to 1 cm in diameter.[27] Since then, multiple trials have likewise shown a decrease in local recurrence if radiation therapy is added to the treatment regimen.[15-17, 27-30] In early stage breast cancer, adjuvant radiotherapy has been shown to reduce the risk of recurrent breast disease by approximately 50%.[31, 32] Nonetheless, radiation can cause short-term side effects such as fatigue and skin irritation, and long-term

changes to skin or breast tissue texture and cosmetic appearance. Radiation can also slightly increase the risk of developing heart disease and there is a very low risk of developing a secondary cancer due to radiation exposure.[33-35]

While adjuvant radiation therapy is currently the standard of care treatment for older women diagnosed with early-stage breast cancer following BCS, recent studies have begun investigating whether de-escalation of adjuvant therapies may be appropriate for certain patients. For example, recent randomized trials indicate that most elderly, estrogen receptor positive patients with T1 N0 breast cancer treated by BCS may not require radiation therapy.[21, 28, 36] Multiple studies have shown a low risk of ipsilateral breast events for selected patients age 65 years or older with early stage (Stage I) breast cancer treated with BCS and adjunctive hormone therapy without standard adjuvant radiotherapy, with local recurrence rates as low as 0.2%.[37] In 2023, Whelan, et al. reported the results of the LUMINA study in which radiotherapy was omitted after BCS in 500 women ≥55 years old with T1N0 (tumor size <2 cm and node negative), grade 1 or 2, Luminal A breast cancer receiving endocrine therapy; the study showed cumulative incidence of local recurrence at 5 years was 2.3%.[38]

However, the relatively short follow-up duration of most literature studies has limitations for assessing the long-term outcomes in breast cancer. The 10-year follow-up data of the PRIME II study, one of the first long-term clinical trials in older breast cancer patients, suggests that for patients aged 65 years or older with low-risk, hormone receptor-positive, node negative breast cancer treated with BCS and adjuvant endocrine therapy, omitting radiotherapy resulted in higher local recurrence.[39] In the study of 1,326 women, the cumulative incidence of local breast cancer recurrence within 10 years was 9.5% in the no-radiotherapy group and 0.9% in the radiotherapy group. In 2019, during the 16th St Gallen International Breast Cancer Conference, the panelists suggested radiotherapy after BCS in women aged 70 years in good health and with substantial life-expectancy while recommending the avoidance of adjuvant radiotherapy in patients aged ≥80 years with stage I disease.[40] Likewise, the NCCN guidelines recommend consideration of radiation omission only for a very select subpopulation of patients.[21]

2.3 Prognosis and Recurrence Risk

The majority of women treated for breast cancer are long-term survivors. Early stage (Stage I) breast cancer has a 99% 5-year relative survival rate.[1] However, following successful treatment of the primary breast cancer, cancer recurrence can present locally, within the ipsilateral breast, regionally within the axillary, paramammary, supraclavicular or cervical lymph nodes, or distantly in solid organs. Recurrence requires additional clinical management and has a negative impact on patient quality of life (QoL).

Patient age, tumor size, multifocality, and tumor biology contribute to clinical outcomes in breast cancer, such as recurrence rate. Independent clinicopathologic factors predictive of local recurrence after BCS include tumor type, tumor grade, ER status, PR status, HER2 overexpression, and Ki-67 index.[29, 41, 42] **Table 2** highlights several key patient and disease related risk factors for breast cancer recurrence and their impact.

Adjuvant treatment choice can also significantly impact risk of recurrence. The overall benefits of adjuvant therapy in women with breast cancer favor treatment even in the subset of patients with

early stage, node-negative, invasive breast cancer without metastasis (T1 N0 M0). According to data from the Surveillance, Epidemiology, and End-Results (SEER) Program, these women represent a large subgroup (approximately 40,000 women annually) of patients with breast cancer in the U.S.[1] The use of hormone therapy adjuvant to lumpectomy and radiation therapy has been shown to have a local recurrence risk as low as 1% at 5-years for some patients.[29, 41, 42] For example, a study by the Cancer and Leukemia Group B (CALGB) (C9343 trial) evaluated 636 women ≥ 70 years old who had clinical stage 1 (T1 N0 M0), ER positive breast cancer treated by lumpectomy to receive Tamoxifen plus radiation therapy (317 women) or Tamoxifen alone (319 women) and found that the rate of local or regional recurrence at 5 years was 1% in the group given tamoxifen plus radiation and 4% in the group given tamoxifen alone. At 10-years follow-up, 98% of patients treated with tamoxifen and radiation therapy were free from local and regional recurrences.[24, 29, 43]

Table 2. Patient and disease related risk factors for breast cancer recurrence.

Factor	Impact on risk of recurrence
Patient age [44-46]	- Higher local recurrence rates have been reported in young women with invasive breast carcinoma, and advancing age is associated with more favorable oncological outcomes. - Older women have been shown to have less aggressive disease and likelihood of recurrence (locoregionally and distantly) at initial diagnosis compared with younger women
Anatomic features [45, 47-49]	Increased risk of recurrence: - High grade, lobular carcinoma - Multifocality - Extensive intraductal component (EIC) - Lymphovascular invasion (LVI)
HR receptor status [50-53]	HR positive: - Less aggressive - Improved oncological outcomes (e.g., DFS and OS rates) - Relatively favorable prognosis
HER receptor status [53, 54]	HER-overexpression: - More aggressive - Poor prognosis without targeted therapy
Luminal subtype [55-58]	Luminal A: - lowest rate of recurrence - tend to develop metastasis late

Recurrence requires additional surgical and adjunctive treatments to manage and may still have negative impacts on long-term outcomes, such as survival. Local recurrences are treated in the standard of care with BCS (lumpectomy) whenever possible. Total mastectomy is standard of care for patients who were previously treated by conservative surgery followed by radiation therapy. Patients who did not receive post-operative irradiation during their initial management should receive full-dose radiotherapy to the chest wall and to the regional lymph nodes if appropriate.[21] Local and regional recurrence of breast cancer is associated with an increased risk of metastases and decreased survival.[59-62] Multiple studies show that, after treatment of invasive breast cancer with BCS, the risk of developing subsequent distant metastases and death is greater for women who experience a local recurrence than for women without a local recurrence.[63-67] This

observation may be an indicator of biologically aggressive tumor biology, suggesting that cancer cells may already have metastasized by the time local recurrence is detected.

Additionally, recurrent breast cancer significantly impairs the QoL of women and their family members with adverse outcomes in physical functioning, bodily pain, and psychological and general health performance.[68-71] QoL issues include psychosocial, medical, and nonmedical problems, which predominate in the initial diagnosis, and later give way to physical sickness, emotional distress, anxiety, confusion, disruption of daily routines, uncertainty, depressed mood, emotional difficulties, physical and bodily pain (beyond that caused by chemotherapy), and existential concern.

3 Regulatory Context

The ProSense System is a cryosurgical ablation device. Cryosurgical devices have been marketed in the U.S. since before the Medical Device Amendments of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1976. Since then, many cryosurgical devices have obtained marketing authorization for general cryogenic destruction of tissue during surgical procedures, including indications for ablation of tumors and benign breast lesions (e.g., fibroadenoma). These authorizations have primarily relied upon bench testing data which validate the technological specifications and performance of the device, and equivalence with previously marketed devices with a long history of clinical use (pre-amendments) for the destruction of tissue.

As of the date of the subject Advisory Committee meeting, there are no FDA-authorized devices, cryosurgical or otherwise, for the definitive surgical treatment of breast cancer in lieu of lumpectomy.

4 ProSense System Background

4.1 Device Description and Operation

The ProSense System (**Figure 1**) 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**). 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). The cooling zone center of the cryoprobes reach a minimum of -170°C.

During a cryoablation procedure for the intended use in this submission, the cryoprobe is inserted via 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 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 controlled by 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 typically takes 20 – 40 minutes.

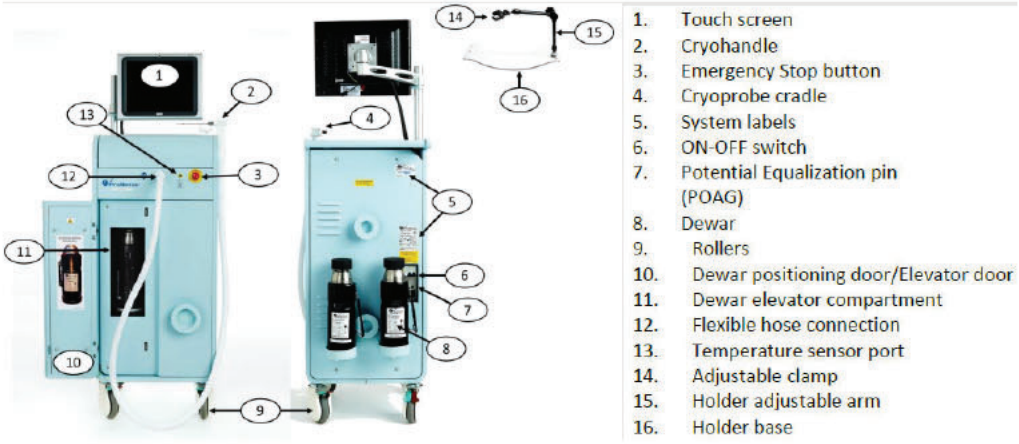

Figure 1. Front and back view of the ProSense System with numbered components.

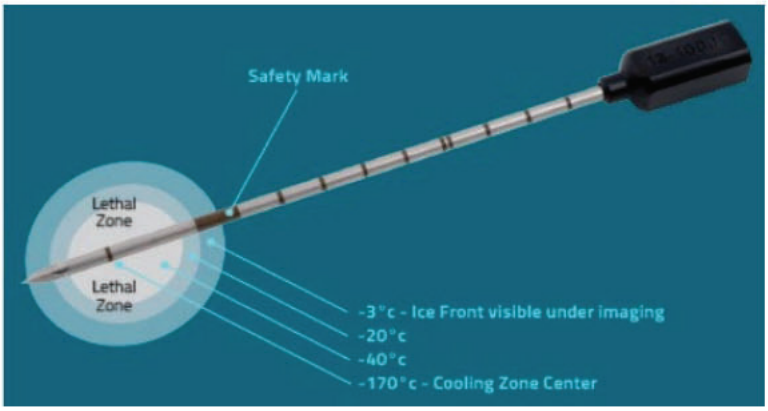

Figure 2. Schematic of the cyoprobe.

4.2 Regulatory History

The ProSense System obtained marketing authorization in K072883, K102360 and 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.

The device was granted breakthrough designation on March 31, 2022 for proposed indications for use in the treatment of patients with T1 invasive breast cancer.

On October 20, 2022, IceCure Medical submitted a De Novo classification request to expand the device indications for use to include treatment of patients with early stage, low risk breast cancer. CDRH determined it would benefit from additional external scientific and clinical perspective on whether the available clinical data demonstrate that the probable benefits of the device outweigh the probable risks prior to making a final decision on the submission.

See **Appendix A** for details regarding the regulatory requirements and policy related to De Novo decision making defined in 21 CFR 860.260 and FDA guidance.

4.3 Proposed Indications for Use

The following Indications for Use (IFU) statement is the subject of the De Novo classification request and panel meeting:

"*ProSense™ cryoablation system is indicated for treatment of patients with early stage, low risk breast cancer* for the treatment of breast cancer with adjuvant endocrine therapy."*

*"*Patients with early stage, low-risk breast cancer are patients ≥60 years of age with prognostic stage 1A defined as unifocal tumor size ≤1.5cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0).*"

Please see **Appendix B** for the full proposed IFU statement, which includes previously cleared indications for the ProSense System.

5 Bench and Preclinical Testing

Since the clearance of K193213, the ProSense System underwent minor changes, including minor design and manufacturing changes. These changes are not expected to have a significant impact on the technical performance of the device. As such, no new bench or preclinical data were necessary to support the De Novo submission.

6 Clinical Data

6.1 Background Clinical Data

IceCure Medical referenced several studies in published literature as background to their pivotal study. FDA evaluated the studies in which breast cancer patients were treated with cryoablation and within approximately 30 days underwent surgical resection and pathology assessment of the resected specimen (referred to herein as '*ablate and resect*' studies) to evaluate the rate of complete ablation.[72-76] The studies are summarized in **Table 3**.

The studies evaluated cryoablation of tumors up to 2 cm in size in patients with invasive breast carcinoma; a small portion of patients had DCIS, lobular carcinoma, colloid carcinoma, and medullary carcinoma. The 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. Typical procedure times were 30-40 minutes. The ProSense System (liquid nitrogen cryoablation) was not used in these studies.

The 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).[72, 75] 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 3. Summary of ablate and resect literature studies referenced by IceCure Medical as background data to the ICE3 pivotal study.[72-76]

Study type	Feasibility
Study method	Ablate and resect
Device	Argon gas-based cryoablation systems (e.g., Visica Cryotherapy System by Sanarus Medical)
Number of patients	Between 9 and 99 depending on 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 cryo-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

6.2 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 System for the treatment of early stage breast cancer, in lieu of lumpectomy, and its impact on local recurrence at 5 years follow up. FDA did not provide input on the study design, endpoints, or analysis plan prior to initiation of the study.

6.2.1 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 4**. Patients were not required to receive endocrine therapy, radiation therapy, or chemotherapy, and received these adjuvant therapies at the discretion of the treating physicians.

Table 4. 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.

6.2.2 Pre-defined Study Endpoints

Primary Endpoint

The primary endpoint was the local recurrence rate (In-Breast Tumor Recurrence 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. FDA was not asked to review the performance goal or censoring methods prior to study initiation.

Sample Size
For sample size determination, IceCure Medical assumed that the local recurrence rate for patients receiving the ProSense 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%. FDA notes that IceCure Medical determined the sample size based on estimating the recurrence rate with ±5% as the half-width of the 95% confidence interval.

6.2.3 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. The cryogenic system was activated according to the

ProSense 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. 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. Treatment times were adjusted to target an ice ball width measurement >35 mm at the end of the first freeze, and an ice ball width measurement >40 mm at the end of the second freeze. Total procedure time was 34.9 minutes on average in the ICE3 study.

At the end of the procedure, the Investigator documented baseline lesion sizes, procedure data, and ice ball measurements in the study data records (eCRF). 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.

6.2.4 Protocol Modifications and Deviations

The clinical protocol underwent multiple modifications after the initiation of the study. The first version of the clinical protocol used in the clinical study was Version 13, dated May 11, 2014. During the study, the protocol was amended to include changes to the eligibility criteria. The most notable changes were related to the inclusion age, removal of requirements related to Ki-67, and addition of requirements related to the nuclear and mitotic scores of the Nottingham grade. See **Appendix C** for the full listing of major protocol modifications related to enrollment criteria.

The number of protocol deviations by type and classification ('major' or 'minor') are summarized in **Table 5**. 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. See **Appendix D** for the full listing of major protocol deviations.

Table 5. 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

6.2.5 Subject Disposition and Baseline Characteristics

The trial screened 212 patients, 206 of which were treated with cryoablation using the ProSense 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) or incomplete treatment (N=3) and their participation withdrawn prior to completing the study. Thus, in total, 131 subjects completed the 60-month follow-up visit. See **Figure 3** for a flowchart of patient disposition. Details regarding the patients excluded by the DSMB are included in **Appendix D**.

The subject demographics and tumor characteristics of all 206 treated subjects are shown in **Table 6**. 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; 79.9% (155 of 194) of subjects received adjuvant treatment.

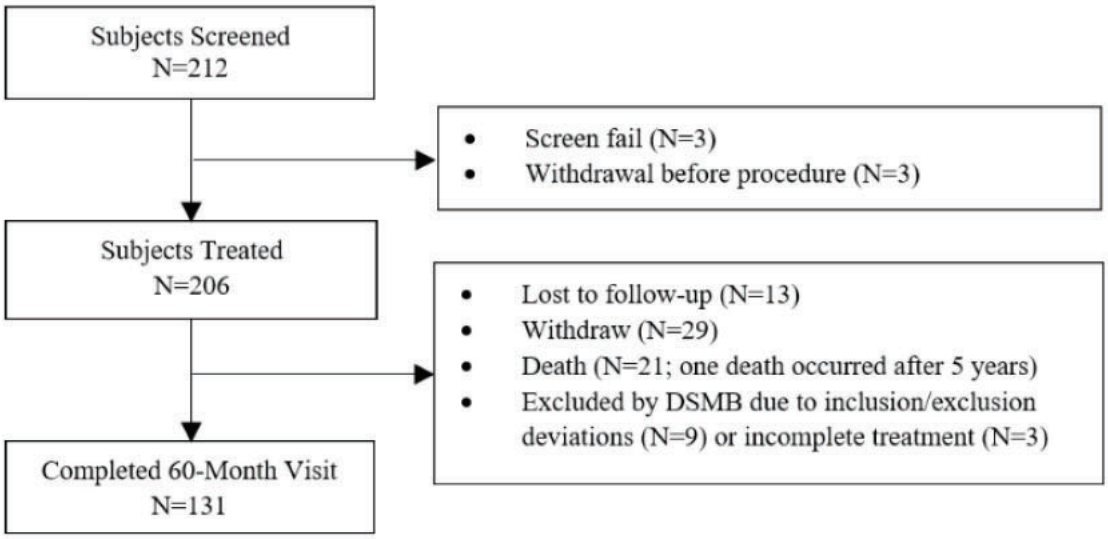

Figure 3. ICE3 patient disposition flowchart.

Table 6. Baseline demographics, tumor characteristics, and adjunctive treatments of all subjects treated with cryoablation using the ProSense System in the ICE3 study (N=206).

	N	% [1]
Gender		
Male	0	0%
Female	206	100%
Ethnicity		
African American	14	7%
Asian	1	1%
Caucasian	160	85%
Hispanic	12	6%

Native American	2	1%
Unknown	17	-
Type of tumor		
Luminal A	188	98%
Luminal B	3	2%
Triple negative	0	0%
Basal like, HER2 Type	0	0%
Unknown	15	-
Estrogen Receptor (ER)		
Positive	194	100%
Negative	0	0%
Unknown	12	-
Progesterone Receptor (PR)		
Positive	180	93%
Negative	14	7%
Unknown	12	-
HER2		
Positive	0	0%
Negative	194	100%
Unknown	12	-
Nottingham Grade [2]		
1	96	49%
2	98	51%
Unknown	12	-
Ki-67		
Ki-67 <14%	93	72%
Ki-67 ≥14%	37	28%
Unknown [3]	76	-
Adjunctive Treatment		
Hormone therapy only	124	64%
Radiation only	3	1.5%
Hormone and radiation therapy	25	13%
Hormone, radiation, and chemotherapy	1	0.5%
No adjunctive treatment or other	41	21%
Unknown	12	-
Age		
55 to 60 years	4	2%
61 to 70 years	47	24%
71 to 80 years	100	52%
81 to 90 years	41	21%
91 to 94 years	2	1%
Unknown	12	-

[1] Percentages are reported out of total subjects with known information. The demographics and patient characteristics of 12 patients excluded by the DSMB were not known by FDA at the time of analysis.
[2] FDA was unable to independently confirm the nuclear grade of 19 patients whose nuclear grade was not reported. 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 protocol, but was later removed. The Ki-67 is unknown for those patients enrolled after the inclusion criterion was removed from the protocol.

6.2.6 ICE3 Study Results

FDA performed an independent analysis of the ICE3 study results to inform the benefit-risk analysis. While the company's assessment provides valuable insights, it did not account for certain limitations of the study design and statistical analysis plan, such as the exclusion of certain patients from the analysis set, exclusion of certain events from the classification of recurrence, and calculation methodology limitations. This executive summary provides FDA's analysis of the study data as well as discussion of the limitations of IceCure Medical's analysis. Differences between FDA and IceCure Medical's analysis methodologies are detailed in **Appendix E.**

Analysis populations
FDA performed an analysis of the ICE3 study results based on all treated patients in the ICE3 study (referred to herein as the Full Analysis Set) and separately based on the per-protocol Primary Analysis Set:

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

The results of FDA's analysis for the Full Analysis Set are summarized in **Table 7**. The results of FDA's analysis for the Primary Analysis Set are summarized in **Table 8**.

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 (CIF) of local recurrences identified in 14 of the 206 treated subjects, and 9.5% (95% CI: 5.7-15.7%) based on Kaplan-Meier (KM) estimation methods. The mean time to recurrence was 35.9 months and the median time to recurrence was 36.5 months.

Of the 14 subjects with local recurrence in the Full Analysis Set, 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, four (4) patients declined further work-up or withdrew from the study, and six (6) patients had no information provided regarding treatment of recurrence, including five patients who were withdrawn by the DSMB before study completion due to inclusion/exclusion deviations or partial cryoablation treatment. 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 were categorized as such by FDA due to evidence of IBTR, but were not categorized as IBTR in IceCure Medical's analysis 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 rate of 6.2% (95% CI: 3.2-11.7%) based on CIF and 6.8% (95% CI: 3.6-12.8%) based on KM. The mean time to recurrence was 47.2 months and the median time to recurrence was 51.6 months. Compared with the Full Analysis Set, this analysis set excludes five recurrences that were identified in the 12 patients excluded by the DSMB.

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 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 of 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.

Note, there are several differences between IceCure Medical's and FDA's independent analyses. A detailed summary of the differences is provided in **Appendix E.** The most significant difference is that FDA determined the results using the Full Analysis Set (N=206) in addition to the per protocol Primary Analysis Set (N=194). Twelve patients were excluded from the Primary Analysis Set of the study due to DSMB assessment of inclusion/exclusion criteria deviations (N=9) or incomplete treatment (N=3). Of those 12 patients, five (5) had local recurrences. FDA includes these 12 patients in an analysis of the full treated population because results from this full analysis set accounts for deviations or non-compliance that might occur in practice during real-world use of the treatment. There are also differences in the number of subjects classified as having IBTR. In both the Full Analysis Set and the Primary Analysis Set, FDA categorized two additional patients as having recurrence compared with IceCure Medical's analysis due to evidence of IBTR; these were not categorized as IBTR in IceCure Medical's analysis due to the patient declining biopsy to confirm imaging findings suspicious for recurrence in one case, and the investigator and/or DSMB categorization as second primary breast cancer in the second case.

Additionally, there are differences in the calculation methodology used between IceCure Medical and FDA. FDA shows both the Kaplan-Meier (KM) method and Cumulative Incidence Function (CIF) calculations for the primary endpoint outcome. The KM method was the pre-specified method in the ICE3 protocol. However, CIF accounts for the competing risk of death in the determination of IBTR rate. There were also differences in the event time and censoring time used

in the KM calculations, which were not pre-specified in the study protocol. Therefore, even for the same number of events, FDA and IceCure Medical's IBTR rates differ.

Table 7. 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).

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 8. 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).

ICE3 Primary Analysis Set (N=194)				
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]	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 System. Safety results were derived from both the Full Analysis Set (N=206) and from the Primary Analysis Set (N=194). A high-level summary is provided here. Complete listings of the SAEs and AEs reported by IceCure Medical in the Clinical Study Report are copied in **Appendix F**.

Within the Primary Analysis Set, 133 SAEs were reported in 65 subjects (33.5%). The majority of SAEs were not considered to be device related. However, all cases of IBTR were considered as serious safety events. As discussed above, fourteen (14) IBTR were observed in the Full Analysis Set. Five (5) of these IBTR were observed among the 12 patients excluded from the Full Analysis Set, resulting in nine (9) cases of IBTR in the Primary Analysis Set. **Table 9** 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, 140 patients of 194 (72.2%) reported 517 AEs. Ninety-three (93) subjects (48.0%) reported 180 procedure-related AEs, the most prevalent of which were bruising in 57 subjects (29%), 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.

Table 9. Serious Adverse Events (SAEs) in the treated population of the ICE3 study (N=206).

SAEs in the Full Analysis Set (N=206)	
	n (%)
Deaths	21 (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	7 (3.4%)
Second primary breast cancer	3 (1.5%)

[1] 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.

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 (111 of 131) 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.

6.2.7 Post-hoc Analyses of ICE3 Study Subpopulations

In addition to the full treated population of the ICE3 study, FDA requested that IceCure Medical provide analyses of two different subpopulations of the overall ICE3 study population. FDA's intent for requesting these subpopulation analyses was to evaluate the outcomes for patients aligned with the proposed IFU statement, and to facilitate comparison with similar, reproducible patient populations in the literature. The subpopulations were defined as follows:

- **Indicated Subpopulation (post-hoc)** (N=120): subpopulation of the primary analysis set requested by FDA and defined post-hoc based on the proposed IFU statement that the intended patients are *"≥60 years of age with prognostic stage 1A defined as unifocal tumor size ≤1.5cm, ER+/PR+/-, HER2-, histological grade 1-2 infiltrating ductal carcinoma (excluding lobular carcinoma, extensive intraductal component, or evidence of lymphovascular invasion), and clinically negative lymph node (N0)"* and receive adjuvant endocrine therapy. The primary difference from the primary analysis set is the exclusion of patients who did not receive hormone therapy and the exclusion of patients with a nuclear score of 3 or unreported Nottingham Grade sub-scores. See **Table 10** for detailed inclusion/exclusion criteria for this analysis subpopulation.

- **LUMINA-aligned Subpopulation (post-hoc)** (N=48): subpopulation of the primary analysis set requested by FDA and defined post-hoc based on patient characteristics defined in the LUMINA literature study.[38] The LUMINA literature study was recognized by FDA as having a reproducible patient population, controlling for all relevant risk factors for recurrence, and a patient population similar to IceCure Medical's indicated population. Subjects were similar in characteristics to the indicated subpopulation, but excluded patients who received radiation therapy and excluded patients without Ki-67<14%. Note, the unavailability of Ki-67 data for many ICE3 study patients is a significant factor contributing to the relatively small number of subjects in this subpopulation. See **Table 11** for detailed inclusion/exclusion criteria for this analysis subpopulation and comparison to the LUMINA study population.

The results of FDA's analysis for the Indicated Subpopulation of the ICE3 study are presented in **Table 12**. FDA's calculated IBTR rate was 2.3% (CIF; 95% CI: 0.6-9.0%) and 2.4% (KM; 95% CI: 0.6-9.6%) for the intended subpopulation based on 2 recurrences identified in this subpopulation (N=120). FDA assessed the ICE3 study population for patient eligibility into the LUMINA-aligned subpopulation and identified only 48 subjects. Given the high levels of uncertainty associated with analyzing a subpopulation of this size, FDA does not present the results for the LUMINA-aligned subpopulation.

The results suggest that the IBTR rate may be lower in the intended subpopulation compared with the overall ICE3 study population. This is to be expected, given that the subpopulations exclude patients who were not treated with adjunctive hormone therapy (both subpopulations), exclude patients with nuclear grade 2-3 or 3 (both subpopulations), and excluded patients unknown Ki-67 or Ki-67≥14% (LUMINA-aligned subpopulation only), which are all expected to negatively impact recurrence rate. However, the ability to draw conclusions from these results is limited by the assumptions used in defining the subpopulations post-hoc and the high uncertainty as indicated by wide confidence intervals.

Table 10. Patient characteristics of the Indicated Subpopulation of the ICE3 study based upon the proposed Indications For Use (IFU) statement.

ICE3 Study Indicated Subpopulation	
INCLUSION	**EXCLUSION**
Unifocal invasive ductal breast carcinoma	Presence of lobular carcinoma, microinvasion or invasive breast carcinoma with extensive intraductal component, lymphovascular invasion, multifocal and/or multicentric breast cancer, multifocal calcifications
Age ≥ 60 years	Age < 60 years
Nottingham grade 1-2; specifically, nuclear and mitotic scores must be ≤2*	Nottingham grade of 3; specifically nuclear and/or mitotic score >2*
Node negative	Node positive
ER positive and/or PR positive, HER2 negative	ER and PR negative, or HER2 positive; presence of luminal B pathology
Tumor size ≤1.5 cm in greatest diameter	Tumor size > 1.5 cm in greatest diameter

Must receive adjuvant endocrine therapy	No adjuvant endocrine therapy

*The proposed IFU does not specify criteria for the Nottingham sub-score components. However, nuclear and mitotic score criteria were used in the definition of the intended subpopulation because they were defined in the inclusion/exclusion criteria of the ICE3 study. Although some patients were enrolled in the ICE3 study in violation of the protocol criteria, these patients were excluded from the subpopulation due to their protocol deviations.

Table 11. Characteristics of patients included in the LUMINA literature study[38] compared with the LUMINA-aligned subpopulation of the ICE3 study.

ICE3 Study LUMINA-aligned subpopulation		
Whelan et al. (LUMINA) patient population[38]		**Comparison between the LUMINA study population and the LUMINA-aligned ICE3 Study Subpopulation**
INCLUSION	**EXCLUSION**	
Invasive breast cancer (ductal, tubular, or mucinous)	Lobular breast cancer, multifocal disease, multicentric disease, extensive intraductal component, lympho-vascular invasion	No differences between the specified criteria and the ICE3 study subpopulation.
Age ≥ 55 years	Age < 55 years	The population enrolled in ICE3 was older than in the LUMINA study. In LUMINA, the median age was 67.1 years (62.9-71.6) with 11.6% of subjects >75 years. In the ICE3 study, the median age was 74.5 years (55-94).
Nottingham grade 1-2	Nottingham grade of 3 No grade reported	The LUMINA study does not specify criteria for the Nottingham sub-score components. However, patients with nuclear grade >3 were excluded from the ICE3 intended subpopulation because of the inclusion/exclusion criteria of the ICE3 study.
Node negative	Node positive	No differences between the specified criteria and the ICE3 study subpopulation.
ER positive (> 1%) PR positive (> 20%) HER2 negative Presence of luminal A pathology	ER negative (≤ 1%) PR negative (≤ 20%) HER2 positive Presence of luminal B pathology	The LUMINA study cited that "if PR not assessed quantitatively, PR 'positive' will be accepted." The ICE3 study did not assess PR quantitatively and included all PR positive subjects. Also, HER2 negativity was used as a surrogate characteristic to define a low-risk population in the ICE3 study, in lieu of luminal status.
Ki-67 < 13.25%	Ki-67 ≥ 13.25% or No Ki-67 reported	The ICE3 CRFs recorded patient Ki-67 as being above or below 14%; this value was considered similar to the LUMINA value of 13.25%. In the ICE3 study, 76 of 206 subjects had unknown Ki-67 and of those with known Ki-67, 37 (28%) had Ki-67≥14%.
Tumor Size < 2.0 cm	Tumor Size ≥ 2.0 cm	The corresponding ICE3 inclusion criterion was tumor size ≤1.5 cm. In the LUMINA study the median tumor size was 1.0 mm. In the ICE3

		study, the mean tumor size was 0.73 mm (range 0.1 – 1.49 mm).
Must receive adjuvant endocrine therapy	No adjuvant endocrine therapy	No differences between the specified criteria and the ICE3 study subpopulation.
No Radiation	Radiation	No differences between the specified criteria and the ICE3 study subpopulation.

Table 12. Local recurrence (IBTR) rate for the Indicated Subpopulation (N=120) post-hoc analysis determined with KM and CIF.

ICE3 Indicated Subpopulation (N=120)			
5-year Outcome Measure	# of events	FDA (KM) Rate (95% CI)[1]	FDA (CIF) Rate (95% CI)[1]
Local recurrence (IBTR)	2	2.4% (0.6-9.6%)	2.3% (0.6-9.0%)

KM=Kaplan-Meier; CIF=Cumulative Incidence Function; IBTR=Ipsilateral Breast Tumor Recurrence
[1]All CIs are nominal values and have no adjustment for multiplicity.

7 Systematic Literature Review and Meta-Analysis

The ICE3 clinical study was a single-arm study with no comparator arm. IceCure Medical derived the performance goal for the primary endpoint (IBTR rate) from a systematic literature review (SLR) and meta-analysis. After the study was completed, the company updated their 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 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 without radiation. 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 the company's SLR and meta-analysis provided valuable information about the outcomes of standard of care, the methodology had limitations which led to inclusion of patients in the meta-analysis who were at a higher risk for recurrence than the indicated population. This is demonstrated by the pre-specified SLR methods which 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, which could inflate the IBTR rate. Additionally, no studies included in IceCure Medical's SLR had radiation treatment arms. Furthermore, IceCure Medical's SLR was limited with respect to the search terms used to identifying potentially relevant articles.

To capture a greater extent of relevant literature articles, while also more stringently applying inclusion/exclusion criteria aligned with the indicated population to derive a meta-estimate, FDA independently conducted a SLR and meta-analysis to inform the comparison of the ICE3 study outcomes with standard of care. The review focused on IBTR at 5 years as a primary outcome.

The definition of DFS has been inconsistent 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). This makes it challenging to compare the DFS results of the ICE3 study with different trials in the literature. Thus, we do not extract DFS information from the SLR. For details on the differences between FDA's and IceCure Medical's SLR methodologies, please refer to **Appendix E**. For full details on the methodology used in FDA's SLR, please refer to **Appendix G**.

7.1 FDA SLR and Meta-Analysis Methods

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 (please see pg. 3, **Appendix G**). A random effects meta-analysis model was used to account for between-study heterogeneity. The FDA searched PubMed/MEDLINE and Embase using targeted search strings. The search identified 3,539 records for screening. For study selection, the inclusion criteria focused on a specific low-risk population, particularly in the meta-analysis.

Inclusion Criteria – Patient Characteristics

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). Literature study populations were matched as closely as possible for those articles selected into the meta-analysis with approximately 98-100% alignment. We note that the patient age target in FDA's SLR of >50 years is younger than the proposed IFU (≥60 years and the average age of the ICE3 population (mean age 74.9 ± 6.9 years; median age 74.5 years). We also note that Ki-67 is not included as a criterion in the IFU and was removed from the enrollment criteria of the ICE3 protocol during the study. Thus, 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.

Inclusion Criteria – Adjuvant Therapies

FDA's SLR required that patients receive adjuvant hormone therapy, per the proposed IFU of the ProSense System. Also, as in the proposed IFU, there were no requirements related to the use of adjuvant radiotherapy. FDA's meta-estimate combines articles with radiotherapy and no-radiotherapy treatment arms and provides a sensitivity analysis evaluating each treatment group separately.

For a detailed comparison between the ICE3 study population, the ICE3 indicated subpopulation, and the FDA SLR criteria, please see **Appendix E**.

7.2 Key Findings of FDA's SLR and Meta-Analysis

7.2.1 Key Qualitative Findings (based on all 25 included studies)

After screening, FDA's SLR included 25 studies in total.[39, 42, 43, 77-79] Of these, 15 studies reported five-year-specific IBTR rates [29, 30, 41-43, 58, 80-88], while 10 studies provided relevant recurrence data over different time periods or in different formats [9, 37, 38, 89-95]. Among the studies reporting five-year IBTR rates, the values ranged from 0% to 12% for different treatment arms.[29, 30, 41-43, 58, 80-88] Notably, five studies reported 0% IBTR rates at five

years or their specified follow-up period.[80-82, 85] Several other studies reported rates below 1% [29, 58, 83], while some showed notable variations between different treatment arms within the same study [41, 42, 84, 85]. For example, Fyles 2004 reported 0.4% for the tamoxifen and radiation arm versus 5.9% for the tamoxifen-only arm.[42] The remaining studies provided valuable data on recurrence rates [29, 37, 43, 90, 92, 93], though not specifically at the five-year mark [9, 37, 38, 89-95]. These studies reported IBTR rates ranging from 0% to 11.57% over various follow-up periods and treatment groups.[9, 37, 38, 89-95] This variability in IBTR rates and reporting methods across studies likely reflects differences in patient populations, treatment modalities, and follow-up durations.

In most studies, both radiotherapy and hormone therapy were widely used, with 21 using radiotherapy [9, 29, 30, 37, 38, 41-43, 58, 80-93, 95] and 23 using hormone therapy [9, 29, 30, 37, 38, 41-43, 58, 80-95]. These treatments were frequently associated with low recurrence rates, suggesting that their use in conjunction with BCS plays a significant role in reducing the risk of in-breast tumor recurrence. Studies that directly compared outcomes with and without radiotherapy, as well as those that examined the impact of hormone therapy, further demonstrated the beneficial effects of these treatments in preventing recurrence after BCS. We note that of the patients enrolled into the Primary Analysis Set of the ICE3 study, approximately 77% received hormone therapy, but only 15% received radiation therapy. In the Indicated Subpopulation of the ICE3 study, all patients were required to receive hormone therapy, and approximately 18% received radiation therapy.

IBTR rates were consistently low across a range of study designs, including 8 randomized controlled trials [29, 30, 41-43, 83, 93, 95] and 13 observational studies [58, 80-82, 84-91, 94], and in various patient populations from different countries (nine studies were from the U.S.) [29, 42, 43, 58, 80, 85, 87-89], four from the United Kingdom [30, 41, 83, 91], three from Italy [82, 86, 95], and nine from other countries [9, 81, 84, 92-94]). Fifteen studies reported a median follow-up of at least five years [9, 29, 30, 37, 41-43, 58, 80, 83, 84, 86-89], and four provided data with follow-up durations of 10 years or more [41, 43, 89, 90]. In the studies with longer-term data low recurrence rates were sustained, supporting evidence of the durability of treatment effects.

This consistency across diverse research methods, adjunctive treatment therapies, geographic settings, and over time reinforces the conclusion that breast-conserving surgery is a safe and effective treatment option for patients with very low-risk breast cancer, particularly those with small, node-negative tumors.

7.2.2 Key Quantitative Findings (meta-analysis of 5 studies/6 distinct cohorts)

FDA's meta-analysis specifically pooled data from five studies [30, 38, 81, 93, 94] that aligned with the proposed IFU for the ProSense System, reflecting a very low-risk patient population adhering to strict selection standards. The studies included in the quantitative analysis had sufficient detail to allow for the extraction of data specific to patient cohorts meeting our inclusion/exclusion criteria. The excluded studies did not permit isolation of a subgroup that precisely matched our parameters, despite containing some eligible patients within their broader study populations. The focus for the meta-analytic cohorts was on ensuring patients followed for 5-year IBTR had early stage, low-risk breast cancer (e.g., T1N0M0, ER/PR+, HER2-) at the time of treatment and excluded patients that had factors which were excluded from the indicated

population such as concomitant chemotherapy, higher-grade tumors, lobular carcinoma, multifocal disease, and lymphovascular invasion. For detailed methodology and documentation of the reasons for inclusion/exclusion of the five studies into the meta-estimate from the full 25 studies included in the SLR, please see **Appendix G**.

A summary table of the 5 studies (6 cohorts) included in FDA's meta-analysis is provided below in **Table 13**. The pooled 5-year IBTR rate from the selected studies was 0.61% (95% CI; 0.10% to 3.50%), reinforcing the effectiveness of BCS in this carefully selected group. While the intention and design of FDA's SLR was not to determine if differences in treatment strategy (i.e., concomitant radiotherapy vs., no concomitant radiotherapy) resulted in different 5-year IBTR outcomes, post-hoc subgroup analyses demonstrated no statistically significant difference in IBTR rates between those who received radiotherapy (0.68%, 95% CI; 0.15% to 2.94%)[30, 81, 93] and those who did not (0.47%, 95% CI; 0.00% to 35.91%) [38, 94], meaning we cannot draw definitive conclusions about the impact of radiotherapy from the meta-estimates. The wide confidence interval and insignificant p value in the no-radiotherapy group suggests uncertainty in this estimate.

High heterogeneity (I^2 = 99.99%, Tau^2 = 2.3583) was observed across the 6 cohorts included in the meta-analysis. This substantial variability is likely due to the inclusion of studies reporting zero IBTR events and differences in patient factors and treatment protocols. The presence of zero-event studies can also significantly impact heterogeneity measures in meta-analyses, especially when dealing with rare events like low IBTR rates in in this very low-risk population. We suggest that findings be interpreted with these limitations in mind.

Note, FDA's meta-estimate is derived from a random effects model, which inherently accounts for variations across different studies and settings. These random effects models yield wider confidence intervals compared to fixed effects models, especially when there is significant variability between studies. FDA does not use the CI limits generated from the random effects model for direct comparison to the clinical study outcomes for several reasons. Random effects models assume variability in true effect sizes across studies, leading to wider CIs that reflect uncertainty rather than performance ranges. CIs indicate likely ranges for true population parameters, not performance thresholds. Their width is influenced by sample size and study heterogeneity, unrelated to performance standards. This can result in extreme and clinically meaningless goals, as seen in the upper CI limit of FDA's meta-estimate for patients receiving BCS without adjuvant radiotherapy ("Without RT"). Moreover, statistical boundaries may not align with clinical significance, and using CI limits as goals can confuse statistical significance with clinical importance.

Additionally, FDA notes that two of the studies below were found to have either moderate or serious risk of bias due to missing data.[83][96] HER2 status was not reported in two studies selected for the quantitative analysis which may cause over-estimation of the rate if higher-risk HER2-positive patients are included.[26][96] Likewise, the Offersen et al. study evaluated locoregional recurrence rate, which may bias the rate upwards due to inclusion of regional recurrences in addition to local recurrences.[95] For further details about the bias risk within the FDA's SLR, please refer to the ROBINS-I assessment of each of the studies (Pg 19, **Appendix**

G). Finally, FDA conducted a sensitivity "leave one out" analyses for our meta-estimate to assess the potential impact of any one study on the meta-estimate (Pg 3, **Appendix G**).

Table 13. Meta-Analysis of 5-Year IBTR Rates from Selected Studies.

Study ID	5-year IBTR Rate (%) (Lower 95% CI - Upper 95% CI)	Initial Sample Size	At Risk at 5-years	No. events at 5-years	Radiation Group
Ciervide 2018 [81][1]	0.0% (0.0% - 0.0%) *	23	16*	0*	Yes
Soyder 2013 [94][1, 2]	0.0% (0.0% - 0.0%) *	16	11*	0*	No
Offersen 2022_1 (WBI Arm) [93][3]	0.7% (0.2% - 1.9%)	434	396	3	Yes
Offersen 2022_2 (PBI Arm) [93][3]	1.2% (0.40% - 2.6%)	431	379	5	Yes
Kunkler 2015_2 (RT Arm) [30][2]	1.3% (0.2% - 2.3%)	658	324	5	Yes
Whelan 2023 [38]	2.3% (1.3% - 3.8%)	500	246	10	No
IBTR Random Effect Weighted Meta-Estimate	0.61% (0.1% - 3.5%)	2062	1372*	23*	Yes & No
With Radiation IBTR Random Effect Weighted Meta-Estimate	0.68% (0.15% - 2.94%)	1546	1115	13	Yes
Without Radiation IBTR Random Effect Weighted Meta-Estimate	0.47% (0.00% - 35.91%)	516	257*	10*	No

[1] Article noted to have moderate or serious risk of bias due to missing data.
[2] HER2 status was not reported in two studies selected for the quantitative analysis.
[3] Includes regional recurrences in the reported locoregional recurrence rate.
* Indicates corrected values where imputation and zero correction were applied for missing or zero event rates. Corrected values are based on SAS output where missing data for number at risk or events were imputed or corrected as described in methods.

7.2.3 SLR Conclusions

IceCure Medical's SLR identified 12 relevant articles of which 11 were included in a meta-estimate. 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. From the qualitative assessment of 25 studies, IBTR rate was consistently low across study designs, geographic locations, and patients receiving different adjunctive therapies, and these were maintained over longer follow-up when reported. The IBTR values ranged from 0% to 12% for different treatment arms and several studies had rates below 1%. In the 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% with the pooled 5-year IBTR rate meta-estimate calculated to be 0.61% (95% CI; 0.10% to 3.50%). However, the overall number of studies included in the meta-estimate with extractable data matching the indicated population was low, and the confidence interval, particularly for the subgroup analysis of patients without adjunctive radiation therapy, was high. Additionally, there are limitations in the ability to align the distribution of patient characteristics (e.g., age) or adjunctive treatments (e.g., radiotherapy) within the SLR population to the distribution within the ICE3 study population.

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

The results of FDA's SLR and meta-estimate are compared to the ICE3 study results in **Table 14.** The estimated IBTR rate for the Full Analysis Set of the ICE3 study was 8.7% (95% CI: 5.2-

14.5%) at the 5-year analysis. However, this analysis population included patients with a variety of adjunctive treatments as shown in the ICE3 study demographics summary table (**Table 6**), including patients treated with hormone therapy, without hormone therapy, with radiation therapy, and without radiation therapy. FDA's SLR was conducted to more closely reflect the intended patient population defined in the proposed IFU, which is limited to those patients receiving adjuvant hormone therapy (note, the proposed IFU does not specify whether patients should receive adjuvant radiation therapy). The IBTR rate of this indicated subpopulation was determined to be 2.3% (95% CI: 0.6-9.0%) in the ICE3 study compared to the 0.61% rate (95% CI: 0.10% to 3.50%) of the FDA SLR and meta-analysis outcomes for the standard of care treatment lumpectomy with adjuvant hormone therapy.

The wide confidence intervals make it challenging to draw conclusions regarding any difference in local recurrence in the indicated population of the ICE3 study compared with the standard of care estimate derived from literature. Additionally, the distribution of patient characteristics (e.g., age) or adjunctive treatments (e.g., radiotherapy) in the enrolled population is challenging to match with the literature comparator which may have a different distribution within the study cohorts.

Table 14. Comparison of 5-year IBTR results from FDA's SLR and the ICE3 study analysis populations of early stage, low-risk patients.

SLR meta-analysis results compared with the ICE3 study results				
5-year outcome	SLR Meta-Analysis (N=2,062) Rate (95% CI)	ICE3 Full Analysis Set (N=206) Rate (95% CI)	ICE3 Primary Analysis Set (N=194) Rate (95% CI)	ICE3 Indicated Subpopulation (N=120) Rate (95% CI)
Local recurrence (IBTR)	0.61% (0.10-3.50%)[1]	8.7% (5.2-14.5%)[2,3]	6.2% (3.2-11.7%)[2,4]	2.3% (0.6-9.0%)[5]

[1] Refers to **Table 13**
[2] Includes two patients categorized by FDA as having evidence of IBTR that were categorized by the DSMB as second primary breast cancer or suspicious for recurrence but not biopsy confirmed.
[3] Refers to **Table 7**, rate calculated by CIF, and CIs are nominal values
[4] Refers to **Table 8**, rate calculated by CIF, and CIs are nominal values
[5] Refers to **Table 12**, rate calculated by CIF, and CIs are nominal values

8 Supplementary Data Collected from Real-World Use of the ProSense System

FDA requested that IceCure Medical provide any relevant and reliable Real-World Data (RWD) regarding use of the ProSense System. FDA defines RWD as "*data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources*" and Real-World Evidence (RWE) as "*the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD*." FDA reviewed the relevance and reliability of the information contained within these data sets based on CDRH's guidance document Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. IceCure Medical provided selected literature reflecting several cohorts, and, separately, results from "post market surveillance" (PMS) conducted by IceCure Medical. The discussion below summarizes

FDA's assessment of whether the information provided is aligned with the above definition and guidance to support the benefit-risk assessment of the ProSense System.

IceCure Medical provided data from 10 different cohorts: seven from clinical literature, two from professional meeting presentations, and one piece of clinical literature reflecting interim analysis of the ICE3 trial. However, not enough information was provided to determine if the data presented was RWD and if so, whether the data were relevant and reliable. Specifically, how the data were collected (i.e., during the routine delivery of health care) and abstracted, how complete and accurate the data were, and how data were linked across data sources was not provided. Therefore, the information provided did not allow FDA to determine the relevance and reliability of the data.

IceCure Medical also provided data collected from 134 patients treated for breast cancer across multiple countries over a ten-year period (2014-2024). However, the data were not found to be independently verifiable; did not include recurrences as device-related adverse events; did not provide information on how short- or long-term safety outcome data were obtained; lacked information on patient inclusion and exclusion criteria into the study population; and had limited information on data abstraction, curation, and aggregation.

Without detailed information on important data elements and study factors to assess the data, it is challenging to determine if these data provided by IceCure Medical are relevant and reliable clinical evidence of the safety of the device for the proposed indication.

9 Benefit-Risk Considerations and Summary

9.1 Benefit

The ICE3 study data was provided to assess clinical benefit for treating patients in the intended use population (i.e., *early stage, low-risk, unifocal breast cancer patients ≥60 years old with histological grade 1-2, HR positive, HER2 negative, node negative disease*) in lieu of lumpectomy. For the proposed IFU, FDA considered the probable benefits of the ProSense System with respect to avoiding a more invasive surgery and with respect to breast cancer treatment outcomes as follows:

<u>Invasive surgery avoidance</u>
The ProSense 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 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 indicating satisfaction with the cosmetic results in those patients providing a rating during follow-up visits. However, as the ICE3 study was a single arm trial, there are no data available that directly compare the adverse events or cosmetic outcomes for lumpectomy of 1.5 cm tumors under local anesthesia with treatment using the ProSense System.

Breast cancer treatment outcomes

Based on FDA's analysis, the ICE3 study demonstrated that patients treated with the ProSense System in lieu of lumpectomy had a 5-year IBTR rate of 8.7% (95% CI: 5.2-14.5%) for the Full Treated Population (N=206). A subpopulation of the overall ICE3 study population aligned with the proposed IFU (those patients receiving adjuvant hormone therapy, among other factors) had a lower IBTR rate of 2.3% (95% CI: 0.6-9.0%). FDA determined that the DFS for the Full Analysis Set was 75.2% (95% CI: 67.7-81.2%; per protocol), the OS was 88.6% (95% CI: 82.8-92.5%), and the Breast Cancer Survival rate was 96.6% (95% CI: 92-98.6%). The probable benefit over standard of care cannot be directly determined due to the single arm design of the ICE3 study. Based on FDA's SLR, standard of care IBTR rates for early stage, low risk breast cancer patients range from 0% to 12% depending on the treatment regimen and patient characteristics. IBTR rates in the literature for patients aged >50 years treated with lumpectomy, adjunctive hormone therapy, and with or without adjunctive radiation therapy, ranged from 0 to 2.3% with the pooled 5-year IBTR rate meta-estimate calculated to be 0.61% (95% CI: 0.10% to 3.50%).

9.2 Risk

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

No surgical specimen for pathology assessment

Without a lumpectomy specimen available for final pathology assessment, patient management decisions rely on the core biopsy results and follow-up imaging after cryoablation treatment. There are risks of relying only on a core biopsy result for pathology, including (1) variability in receptor status between the core and the final, and (2) insufficient tissue available for analysis of molecular receptors, genetic signature analysis, and Ki-67 index profiling. The assessment of pathology information is important for standard of care treatment decisions. Additionally, cryoablation does not allow the tumor margin status to be evaluated by histopathology after treatment. Assessment of cryodestruction relies on the quality and sensitivity of the imaging modality used during and after treatment, including mammography and MRI for detection of recurrent disease.

Breast cancer treatment outcomes

Based on the available data from FDA's SLR and meta-analysis, the IBTR rate demonstrated in the ICE3 study is higher than that of patients receiving the current standard of care lumpectomy procedure with adjuvant hormone therapy.

The significance of local recurrence rate is notable. After treatment of invasive breast cancer with BCS, the risk of developing subsequent distant metastases and death is greater for women who experience a local recurrence than for women without a local recurrence.[63-67] More importantly, the consequences from breast cancer recurrence involve multi-modal treatment for recurrence, including: surgery to resect the recurrence, typically involving a total mastectomy; systemic therapy (typically chemotherapy); and/or radiation therapy. Patients diagnosed with recurrence experience a decline in functional status[71] and quality of life (QoL) issues, such as psychosocial, medical, and nonmedical problems, which predominate in the initial diagnosis, and may give way to physical sickness, emotional distress, anxiety, confusion, disruption of daily routines, uncertainty, depressed mood, emotional difficulties, physical and bodily pain (beyond that caused by chemotherapy), and existential concerns.[68-71]

Procedure-related risks
Besides IBTR, the most prevalent procedure-related AEs were localized edema, bruising, and pain.

9.3 Uncertainty in the Benefit-Risk Assessment

There is uncertainty in the benefit-risk assessment due to limitations of the ICE3 study and the methods used to compare the study results to standard of care outcomes for comparable patient populations. The study did not have a control arm, which makes comparison of the device safety and effectiveness to standard of care challenging. The key uncertainties in the data related to this comparison are discussed in the paragraphs below in the context of four main categories: reproducibility of the patient population, wide confidence intervals, availability of a reliable literature-derived comparator, and unknown rate of complete ablation.

Reproducibility of the patient population
Reproducibility of the patient population is important to draw comparisons between the results of the single arm ICE3 study and standard of care outcomes for comparable patient populations in the available literature. Reproducibility is also important to inform a specific intended use population for whom the probable benefits are expected to outweigh the probable risks, and to mitigate uncertainty related to generalizing the results of the study to real world use. FDA identified limitations in the reproducibility of the ICE3 study patient population, including the following:

1. Not all risk factors for recurrence are controlled for within the ICE3 enrollment criteria. For example, adjuvant treatments like hormone therapy and radiation therapy have a significant impact on treatment outcomes, yet the ICE3 study did not have enrollment criteria related to these treatments. The majority of patients enrolled in the ICE3 study received adjuvant hormone therapy only (64%), with an additional 12% receiving both hormone therapy and radiation therapy; some patients received neither adjuvant therapy. In FDA's SLR and meta-analysis, four of the six cohorts received radiation therapy whereas only 15% of the ICE3 study population received radiation therapy. The SLR had high heterogeneity in the no-radiotherapy sensitivity analysis. Without a control arm of the ICE3 study with a similar distribution of adjunctive treatment regimens, it is challenging to compare the results of the study to standard of care outcomes.

   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. FDA notes that while the proposed indications for use describe an intended use in patients ≥60 years of age, the median age of the ICE3 trial was 74.5 years. The SLR evaluated patients aged >50 years. Some studies have shown that a higher age may have a relatively lower risk of recurrence due to a likelihood of death by competing risks and the fact that older patients tend to present with less aggressive disease.[44]

2. Protocol revisions and deviations add uncertainty to the reproducibility of the ICE3 study population. The clinical study protocol was modified during study enrollment, including revisions to the eligibility criteria. Moreover, the study included 448 protocol deviations for 157 subjects, including enrolling and treating subjects that did not meet the eligibility criteria,

among others. After enrollment and treatment, a portion of these patients (12 subjects) were later excluded by the DSMB and therefore from IceCure Medical's evaluation of the primary endpoint. Protocol changes and deviations can contribute to uncertainty in the study findings.

Variability due to limited sample size

The sample size (N=206) is small relative to the low anticipated recurrence rate for the intended patient population, resulting in high variability in the estimation of event rate. The two-sided 95% confidence interval for the IBTR rate spanned a nearly 10% range. When the overall study population was further refined in post-hoc analyses to reproducible characteristics, the resulting intended subpopulation and LUMINA-aligned subpopulation were significantly smaller (N=120 and N=48, respectively), making it challenging to draw clinically meaningful conclusions. Additionally, 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. Therefore, a smaller number of subjects available at the 60-month study endpoint contributes to additional variability in the estimation of event rate.

Availability of a literature comparator

FDA identified 25 studies that were appropriate to perform a qualitative assessment of the IBTR rate for standard of care. However, only five studies (six patient cohorts) met the most stringent inclusion/exclusion criteria comparable to the intended patient population for inclusion into the quantitative meta-estimate, and two of these studies had less than 25 patients. The limited number of large studies available for a meta-estimate comparator to the intended patient population creates significant uncertainty in the comparison of the ICE3 study results to standard of care outcomes. As discussed above, 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).

Unknown complete ablation rate

Feasibility studies using an ablate and resect design to estimate complete ablation rate were not conducted with the ProSense System. The ablate and follow ICE3 pivotal study does not allow for histopathology to confirm margin status after treatment with the ProSense System, and without accurate imaging modalities to confirm complete ablation, the complete ablation rate is uncertain.

10 Conclusions

The ProSense System offers a minimally invasive method of ablating localized breast tumors ≤1.5 cm in early stage, low-risk breast cancer patients. The treatment can be performed under local anesthesia as an alternative to the standard of care lumpectomy. Lumpectomy of 1.5 cm tumors is a low-risk procedure, and is highly effective, particularly in early stage breast cancer populations due to the less aggressive nature of the disease. IBTR rates in the literature for those patients aged >50 years old treated with lumpectomy, adjunctive hormone therapy, and with or without adjunctive radiation therapy, ranged from 0 to 2.3% with the pooled 5-year IBTR rate meta-estimate calculated to be 0.61% (95% CI: 0.10% to 3.50%). The ICE3 study data shows an IBTR rate of 2.3% (95% CI: 0.6-9.0%) for patients treated with the ProSense System and adjunctive hormone therapy (post-hoc indicated subpopulation analysis). However, a significant number of limitations in the analysis raises uncertainty in the comparison.

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