Discussion Questions

for the General and Plastic Surgery Devices Advisory Panel

November 7, 2024

De Novo Classification Request for
IceCure Medical, Ltd. ProSense Cryoablation System
based on data from the ICE3 Study

Background

IceCure Medical referenced several '*ablate and resect*' literature studies which reported effectiveness rates of complete tumor necrosis ranging from 76% to 100%, depending on tumor size. Reference FDA's Executive Summary **Table 3**.

Q1. Please comment on the strengths and limitations of standard of care imaging technology (e.g., mammography, ultrasound, MRI) to accurately characterize the tumor size and extent prior to surgical or cryoablation treatment in early stage, low-risk breast cancer patients.

ICE3 Study Design and Population

The ICE3 study was a single-arm, nonrandomized trial. Effectiveness of the ProSense System was evaluated based on a primary effectiveness endpoint of Ipsilateral Breast Tumor Recurrence (IBTR) rate at five years follow-up. The study protocol pre-specified that if the upper limit of the two-sided 95% confidence interval is less than 10%, the study will be considered successful.

The study enrolled and treated 206 women with early stage, low-risk breast cancer, defined as patients with unifocal primary disease, lymph node negative, tumor size ≤1.5 cm, Nottingham Grade 1-2, ER positive and/or PR positive, and HER2 negative. The mean age of patients was 74.9 ± 6.9 years. Patients received adjuvant therapies at the discretion of the treating physicians. Reference FDA's Executive Summary **Table 6** for ICE3 study patient characteristics.

Q2. Please discuss the strengths and limitations of the single-arm, nonrandomized study design using a literature-derived performance goal for the primary endpoint IBTR rate. In particular, please comment on:

   a. The 10% performance goal; and

   b. The reproducibility of the patient population in the ICE3 study with respect to relevant risk factors for local recurrence (IBTR).

ICE3 Study Results

In the ICE3 study, 206 patients were treated with the ProSense System, and 131 completed the 60-month follow-up visit. FDA performed an analysis of the study results based on three analysis populations (see Analysis Populations Reference Sheet at the end of this document). The primary endpoint results for each analysis population are summarized in the following table (please refer to **Table 7**, **Table 8**, and **Table 12** of FDA's Executive Summary). Note, FDA's analysis includes two patients categorized by FDA as having evidence of local recurrence that were categorized by the DSMB as second primary breast cancer or suspicious for recurrence but not biopsy confirmed.

Summary of 5-year outcomes in the ICE3 study analysis populations				
5-year outcome	Event Type	# of subjects	FDA Rate (95% CI)[1,2]	IceCure Medical Rate (95% CI UB)[3]
ICE3 Full Analysis Set (N=206)				
IBTR	Local recurrence	FDA: 14 IceCure: N/A	8.7% (5.2-14.5%)	-
ICE3 Primary Analysis Set (N=194)				
IBTR	Local recurrence	FDA: 9 IceCure: 7	6.2% (3.2-11.7%)	4.3% (UB 8.7%)
ICE3 Indicated Subpopulation (N=120) [4]				
IBTR	Local recurrence	FDA: 2 IceCure: 2	2.3% (0.6-9.0%)	1.95% (UB 7.6%)

[1] All CIs have no adjustment for multiplicity. FDA considers CIs presented in the table as nominal values.
[2] Rate is based on Cumulative Incidence Function (CIF)
[3] Rate is based on Kaplan-Meier method.
[4] ICE3 study inclusion criterion 1.c. (see Table on p.5) required that Nottingham score is 1-2 with nuclear and mitotic scores ≤ 2. For n=27 subjects, nuclear score does not meet the criteria of ≤ 2. These n=27 subjects are not accounted for by FDA as part of the Indicated Subpopulation (n=120).

Q3. Please comment on the strengths and limitations of each analysis population and subpopulation for determining the benefit versus risk of the ProSense System for the proposed IFU. In particular, please comment on:

   a. the relative heterogeneity of subjects with respect to risk factors for recurrence;

   b. alignment with the proposed indications for use;

   c. adequacy of the sample sizes and corresponding uncertainty

PRISMA Systematic Literature Review and Meta-Analysis Comparator

FDA and IceCure Medical each conducted a Systematic Literature Review (SLR) and meta-analysis to inform the comparison of the ICE3 study outcomes with standard of care. The results are summarized in the table below. IceCure Medical's SLR meta-estimate was derived from 11 studies of patients treated with lumpectomy and without radiotherapy. A sensitivity analysis was performed for patients treated with lumpectomy and endocrine therapy (and no radiotherapy). To

maximize the number of studies included, IceCure Medical's SLR required that only 75% of patients in each article align with the meta-analysis criteria, and as a result, included cohorts with risk factors for recurrence not present in the indicated population, such as lobular carcinoma, high tumor grade, multifocal tumors, and lymphovascular invasion. FDA's SLR evaluated patients treated with lumpectomy, endocrine therapy, and had no restrictions related to use of radiation therapy. FDA's meta-analysis was derived from five studies that stringently aligned with the meta-analysis criteria. Reference FDA's Executive Summary **Table 13**. Both SLRs have 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.

SLR meta-analysis results compared with the ICE3 study results			
5-year outcome	IceCure Medical SLR Meta-Analysis	FDA SLR Meta-Analysis	ICE3 Study Indicated Subpopulation (N=120)
	Lumpectomy + endocrine therapy, no radiotherapy*	Lumpectomy + endocrine therapy	Lumpectomy + endocrine therapy*
IBTR rate	2.82% 95% CI UB 4.83%	0.61% 95% CI: 0.10-3.50%	2.3% 95% CI: 0.6-9.0%

*17% of the ICE3 indicated subpopulation received radiotherapy, which was excluded from IceCure Medical's SLR.

Q4. Please discuss the overall clinical significance of the effectiveness results of the ICE3 study compared to the SLR and meta-estimate results.

Safety

The most prevalent procedure-related adverse events in the ICE3 study were bruising in 57 subjects (29%), pain in 36 subjects (18.6%), and localized edema in 35 subjects (18.0%). The ICE3 study also showed that approximately 99% of patient respondents were 'satisfied' or 'very satisfied' with the cosmetic outcome of the procedure based on a 5-point scale. Due to the single-arm design of the study, a direct comparison of procedure-related adverse events, quality of life, and cosmetic satisfaction with the ProSense System versus standard of care is not available.

Additionally, real-time visualization of tumor ablation during treatment and routine annual mammography for identifying residual tumor and monitoring recurrence are important aspects of use of this device.

Q5. Please comment on how this informs benefit and risk of the ProSense System.

Benefit-Risk

If granted marketing authorization, the ProSense System would be the first non-surgical alternative to the current standard of care lumpectomy. This treatment relies on accurately characterizing lesion size and extent by imaging prior to cryoablation, and real-time evaluation of tumor destruction, given that no specimen is acquired for histopathological evaluation of tumor margins after the procedure is completed.

Q6. Please discuss the quality of life benefits of surgery avoidance relative to the quality of life risks of breast cancer recurrence for the intended patient population.

Q7. Given the totality of evidence presented regarding the safety and effectiveness of the ProSense System, please comment on the overall benefit-risk profile of the device for the proposed indications for use in the treatment of early stage, low-risk breast cancer in lieu of lumpectomy.

Voting Question:

Considering the data from the ICE3 trial and the reported outcomes in the literature for standard of care, do the benefits of the IceCure Medical, Ltd. ProSense Cryoablation System outweigh the risk for the proposed Indications for Use?

Patient Populations Reference Sheet

Proposed Indications for Use

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

**Early stage, low-risk breast cancer patients are patients ≥60 years of age with 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)."*

ICE3 Study Enrollment Criteria

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, but was subsequently removed. The investigators and Data Safety Monitoring Board (DSMB) recommended that the Nottingham score and its components ((i.e. tubule formation score, nuclear score, and mitotic score) define the level of risk and are sufficient to replace the Ki-67.

Analysis Populations

- **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 those excluded by the Data Safety Monitoring Board (DSMB) due to certain violations of the ICE3 protocol inclusion/exclusion criteria or incomplete treatment.
- **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 criteria (above). The primary difference from the primary analysis set is the exclusion of patients who did not receive endocrine therapy and exclusion of patients with a nuclear score of 3 or unreported Nottingham Grade sub-scores.