

Appendix B – ICE3 Full Safety Results

1. Primary Analysis Set**1.1. All Adverse Events**

As shown below, 140 subjects reported 517 adverse events. There were 180 procedure related adverse events reported by 193 subjects and 59 subjects reported 127 serious adverse events. There were four (4) serious procedure related adverse events, three (3) being local recurrence and one (1) being metastatic breast cancer. The majority of procedure-related events were mild in severity.

In total, there were 21 deaths (10.8%) during the follow-up period; two were verified as related to breast cancer (1.03%). The estimated rate of breast cancer survival was high, 96.7% at 5 years. See Appendix A for more information on reason for death.

Table 1-1: ICE3 Clinical Study Adverse Event Summary - Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
Adverse Events			
All	517	140	72.2%
Procedure Related	180	93	47.9%
Serious Adverse Events			
All	127	59	30.4%
Procedure Related	4	3	1.5%
Adverse Events by Severity			
Mild	333	108	55.7%
Moderate	92	52	26.8%
Severe	92	47	24.2%
Serious Adverse Events by Severity			
Moderate	35	25	12.9%
Severe	87	42	21.6%
Deaths			
All	21	21	10.8%
† Total number of events without regard to length of follow-up. ‡ Number of subjects experiencing event without regard to length of follow-up. ° Percentage of subjects experiencing specific event without regard to length of follow-up. Procedure relationship: Remotely, Possible, Probable, Unknown. Source: Table 5_1 AE Summary_FAS v2.sas; Analyzed: 09JUN2024			

In total, 517 adverse events were reported by 140 subjects. Adverse events listed by system organ class and preferred term can be seen below (**Table 1-2**).

Table 1-2: ICE3 Clinical Study All Adverse Events - Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
All Events	517	140	72.2%
Blood and lymphatic system disorders	7	6	3.1%
Anemia	1	1	0.5%
Febrile Neutropenia	2	2	1.0%
Leukocytosis	2	1	0.5%
Lymph node pain	2	2	1.0%
Cardiac disorders	23	17	8.8%
Acute coronary syndrome	1	1	0.5%
Aortic valve disease	1	1	0.5%
Atrial fibrillation	4	3	1.5%
Atrial flutter	1	1	0.5%
Atrioventricular Block Complete	1	1	0.5%
Cardiac arrest	2	2	1.0%
Chest pain - cardiac	2	1	0.5%
Heart failure	5	4	2.1%
Myocardial infarction	2	2	1.0%
Palpitations	3	3	1.5%
Sick sinus syndrome	1	1	0.5%
Ear and labyrinth disorders	5	3	1.5%
Ear Pain	1	1	0.5%
Hearing impaired	2	2	1.0%
Tinnitus	1	1	0.5%
Vestibular Disorder	1	1	0.5%
Eye disorders	2	2	1.0%
Cataract	1	1	0.5%
Macular degeneration	1	1	0.5%
Gastrointestinal disorders	23	18	9.3%
Abdominal Distension	1	1	0.5%
Abdominal pain	4	4	2.1%
Colitis	1	1	0.5%
Constipation	7	6	3.1%
Diarrhea	3	3	1.5%
Duodenal hemorrhage	1	1	0.5%
Dyspepsia	1	1	0.5%
Dysphagia	1	1	0.5%
Obstruction gastric	2	1	0.5%
Sigmoid diverticulitis	1	1	0.5%
Small intestinal obstruction	1	1	0.5%
General disorders and administration site conditions	125	81	41.8%
COVID	3	2	1.0%
Chills	1	1	0.5%
Death NOS	3	3	1.5%
Edema limbs	2	2	1.0%
Edema of limbs	1	1	0.5%
Fatigue	15	14	7.2%
Heat sensation	2	1	0.5%
Infusion site extravasation	1	1	0.5%
Injection site reaction	11	10	5.2%
Irritability	1	1	0.5%
Localized edema	38	37	19.1%
Malaise	1	1	0.5%
Multi-organ failure	1	1	0.5%
Non-cardiac chest pain	2	2	1.0%
Pain	43	39	20.1%
Infections and infestations	31	21	10.8%
Endocarditis infective	1	1	0.5%
Lung infection	6	6	3.1%
Papulopustular Rash	1	1	0.5%
Rash Pustular	1	1	0.5%
Sepsis	3	3	1.5%
Skin infection	15	9	4.6%
Upper respiratory infection	1	1	0.5%
Urinary tract infection	3	3	1.5%

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	Events†	Subjs‡	%°
Injury, poisoning and procedural complications	77	67	34.5%
Bruising	57	57	29.4%
Burn	4	4	2.1%
Dermatitis radiation	3	3	1.5%
Fall	8	8	4.1%
Fracture	3	3	1.5%
Hip fracture	1	1	0.5%
postoperative hemorrhage	1	1	0.5%
Investigations	4	3	1.5%
Cholesterol high	1	1	0.5%
Weight loss	3	2	1.0%
Metabolism and nutrition disorders	5	5	2.6%
Anorexia	1	1	0.5%
Hypercalcemia	1	1	0.5%
Hypertriglyceridemia	1	1	0.5%
Hypokalemia	1	1	0.5%
Malnutrition	1	1	0.5%
Musculoskeletal and connective tissue disorders	45	28	14.4%
Arthralgia	16	15	7.7%
Arthritis	3	3	1.5%
Back pain	7	6	3.1%
Flank Pain	1	1	0.5%
Generalized muscle weakness	1	1	0.5%
Myalgia	4	3	1.5%
Neck pain	2	2	1.0%
Osteoporosis	1	1	0.5%
Pain in extremity	7	6	3.1%
Rhabdomyolysis	1	1	0.5%
Superficial soft tissue fibrosis	2	1	0.5%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25	24	12.4%
Acute Myeloid Leukemia	1	1	0.5%
Benign Neoplasm	1	1	0.5%
DCIS Left Breast	1	1	0.5%
Diffuse Metastatic disease to the bones	1	1	0.5%
Endometrial Cancer	2	2	1.0%
Endometrial Cyst	1	1	0.5%
Epidermal Inclusion Cyst	1	1	0.5%
Hepatocellular carcinoma	1	1	0.5%
Kidney cancer	1	1	0.5%
Local recurrence	7	7	3.6%
Lung Adenocarcinoma	1	1	0.5%
Meningioma	1	1	0.5%
Metastatic breast cancer	1	1	0.5%
Mole	1	1	0.5%
Non-small cell lung cancer	1	1	0.5%
Second primary BC	3	3	1.5%
Nervous system disorders	27	22	11.3%
Altered mental status	1	1	0.5%
Dizziness	4	3	1.5%
Encephalopathy	1	1	0.5%
Headache	3	3	1.5%
Intracranial hemorrhage	1	1	0.5%
Memory impairment	6	6	3.1%
Paresthesia	2	2	1.0%
Peripheral sensory neuropathy	1	1	0.5%
Presyncope	1	1	0.5%
Seizure	1	1	0.5%
Spasticity	1	1	0.5%
Stroke	2	2	1.0%
Syncope	1	1	0.5%
Thoracic stenosis	1	1	0.5%
Transient ischemic attacks	1	1	0.5%

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	Events†	Subjs‡	%°
Psychiatric disorders	14	12	6.2%
Anxiety	6	6	3.1%
Depression	3	3	1.5%
Insomnia	4	4	2.1%
Psychiatric disorders - Other Mild	1	1	0.5%
Renal and urinary disorders	11	9	4.6%
Acute kidney injury	4	4	2.1%
Hematuria	1	1	0.5%
Urinary frequency	2	2	1.0%
Urinary incontinence	3	2	1.0%
urinary tract pain	1	1	0.5%
Reproductive system and breast disorders	6	4	2.1%
Breast twitches	1	1	0.5%
Dimpling	1	1	0.5%
Dyspareunia	1	1	0.5%
Tethering	1	1	0.5%
Vaginal dryness	2	2	1.0%
Respiratory, thoracic and mediastinal disorders	37	22	11.3%
Aspiration	2	1	0.5%
Atelectasis	1	1	0.5%
COPD	2	2	1.0%
Cough	6	5	2.6%
Dyspnea	11	8	4.1%
Emphysema	1	1	0.5%
Hypoxia	2	1	0.5%
Nasal congestion	1	1	0.5%
Pleural effusion	6	5	2.6%
Pulmonary edema	1	1	0.5%
Respiratory failure	4	4	2.1%
Skin and subcutaneous tissue disorders	21	17	8.8%
Alopecia	1	1	0.5%
Body odor	1	1	0.5%
Drainage	1	1	0.5%
Dry skin	1	1	0.5%
Erythema multiforme	7	6	3.1%
Hirsutism	1	1	0.5%
Pruritus	6	6	3.1%
Rash acneiform	1	1	0.5%
Skin hyperpigmentation	1	1	0.5%
Skin rash	1	1	0.5%
Surgical and medical procedures	2	2	1.0%
Herniorrhaphy /Hernioplasty	1	1	0.5%
Yellow discharge	1	1	0.5%
Vascular disorders	27	25	12.9%
Bilateral Carotid Stenosis	1	1	0.5%
Flushing	1	1	0.5%
Hematoma	9	9	4.6%
Hot flashes	9	9	4.6%
Hypertension	4	4	2.1%
Thromboembolic event	3	3	1.5%
† Total number of events without regard to length of follow-up. ‡ Number of subjects experiencing event without regard to length of follow-up. ° Percentage of subjects experiencing specific event without regard to length of follow-up. Procedure relationship: Remotely, Possible, Probable, Unknown. Adverse events with missing date are analyzed as relative day 1. Source: Tables Safety_FAS.sas; Analyzed: 09JUN2024			

A listing of all adverse events by AE code and timecourse can be found below (Table 1-3).

Table 1-3: ICE3 Clinical Study All Adverse Events by Timecourse - Primary Analysis Set (N=194)

	0	1-30	31-60	61-180	181-365	366-730	731-1095	1096-1460	1461-1825	>1825	Total
All Events	66	114	8	44	90	68	42	32	39	14	517
Blood and lymphatic system disorders	0	0	2	1	1	1	0	0	2	0	7
Anemia	0	0	0	0	0	0	0	0	1	0	1
Febrile Neutropenia	0	0	0	1	0	0	0	0	1	0	2
Leukocytosis	0	0	2	0	0	0	0	0	0	0	2
Lymph node pain	0	0	0	0	1	1	0	0	0	0	2
Cardiac disorders	0	0	0	0	1	5	5	8	2	2	23
Acute coronary syndrome	0	0	0	0	0	0	0	1	0	0	1
Aortic valve disease	0	0	0	0	0	0	1	0	0	0	1
Atrial fibrillation	0	0	0	0	0	1	1	0	1	1	4
Atrial flutter	0	0	0	0	0	0	0	1	0	0	1
Atrioventricular Block Complete	0	0	0	0	0	0	1	0	0	0	1
Cardiac arrest	0	0	0	0	0	0	1	1	0	0	2
Chest pain - cardiac	0	0	0	0	0	0	0	1	0	1	2
Heart failure	0	0	0	0	1	0	1	2	1	0	5
Myocardial infarction	0	0	0	0	0	1	0	1	0	0	2
Palpitations	0	0	0	0	0	3	0	0	0	0	3
Sick sinus syndrome	0	0	0	0	0	0	0	1	0	0	1
Ear and labyrinth disorders	0	0	0	1	0	4	0	0	0	0	5
Ear Pain	0	0	0	0	0	1	0	0	0	0	1
Hearing impaired	0	0	0	0	0	2	0	0	0	0	2
Tinnitus	0	0	0	0	0	1	0	0	0	0	1
Vestibular Disorder	0	0	0	1	0	0	0	0	0	0	1
Eye disorders	0	0	0	1	0	1	0	0	0	0	2
Cataract	0	0	0	0	0	1	0	0	0	0	1
Macular degeneration	0	0	0	1	0	0	0	0	0	0	1
Gastrointestinal disorders	0	0	2	3	6	2	2	4	4	0	23
Abdominal Distension	0	0	0	1	0	0	0	0	0	0	1
Abdominal pain	0	0	0	0	2	0	1	1	0	0	4
Colitis	0	0	0	0	1	0	0	0	0	0	1
Constipation	0	0	2	2	1	1	0	0	1	0	7
Diarrhea	0	0	0	0	2	0	1	0	0	0	3
Duodenal hemorrhage	0	0	0	0	0	0	0	1	0	0	1
Dyspepsia	0	0	0	0	0	1	0	0	0	0	1
Dysphagia	0	0	0	0	0	0	0	0	1	0	1
Obstruction gastric	0	0	0	0	0	0	0	2	0	0	2
Sigmoid diverticulitis	0	0	0	0	0	0	0	0	1	0	1
Small intestinal obstruction	0	0	0	0	0	0	0	0	1	0	1
General disorders and administration site conditions	34	50	1	5	18	7	3	3	4	0	125
COVID	0	0	0	0	0	0	0	1	2	0	3
Chills	0	0	0	0	1	0	0	0	0	0	1

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	0	1-30	31-60	61-180	181-365	366-730	731-1095	1096-1460	1461-1825	>1825	Total
Death NOS	0	0	0	0	0	0	2	1	0	0	3
Edema limbs	0	0	0	0	0	1	0	0	1	0	2
Edema of limbs	0	0	0	1	0	0	0	0	0	0	1
Fatigue	1	2	0	2	7	1	1	0	1	0	15
Heat sensation	0	1	0	0	0	1	0	0	0	0	2
Infusion site extravasation	0	1	0	0	0	0	0	0	0	0	1
Injection site reaction	3	6	0	0	0	2	0	0	0	0	11
Irritability	0	0	0	0	1	0	0	0	0	0	1
Localized edema	11	24	0	1	2	0	0	0	0	0	38
Malaise	0	0	0	0	1	0	0	0	0	0	1
Multi-organ failure	0	0	0	0	0	1	0	0	0	0	1
Non-cardiac chest pain	1	0	0	0	1	0	0	0	0	0	2
Pain	18	16	1	1	5	1	0	1	0	0	43
Infections and infestations	0	0	1	7	7	5	3	2	4	2	31
Endocarditis infective	0	0	0	0	0	0	1	0	0	0	1
Lung infection	0	0	1	0	0	0	0	2	1	2	6
Papulopustular Rash	0	0	0	1	0	0	0	0	0	0	1
Rash Pustular	0	0	0	0	1	0	0	0	0	0	1
Sepsis	0	0	0	0	0	1	0	0	2	0	3
Skin infection	0	0	0	5	5	4	1	0	0	0	15
Upper respiratory infection	0	0	0	0	0	0	0	0	1	0	1
Urinary tract infection	0	0	0	1	1	0	1	0	0	0	3
Injury, poisoning and procedural complications	18	45	1	3	4	1	1	1	2	1	77
Bruising	16	41	0	0	0	0	0	0	0	0	57
Burn	1	3	0	0	0	0	0	0	0	0	4
Dermatitis radiation	0	1	1	0	1	0	0	0	0	0	3
Fall	0	0	0	2	2	0	1	0	2	1	8
Fracture	0	0	0	1	1	1	0	0	0	0	3
Hip fracture	0	0	0	0	0	0	0	1	0	0	1
postoperative hemorrhage	1	0	0	0	0	0	0	0	0	0	1
Investigations	0	0	0	1	1	0	1	1	0	0	4
Cholesterol high	0	0	0	0	0	0	0	1	0	0	1
Weight loss	0	0	0	1	1	0	1	0	0	0	3
Metabolism and nutrition disorders	0	0	0	0	1	0	1	2	0	1	5
Anorexia	0	0	0	0	0	0	1	0	0	0	1
Hypercalcemia	0	0	0	0	1	0	0	0	0	0	1
Hypertriglyceridemia	0	0	0	0	0	0	0	1	0	0	1
Hypokalemia	0	0	0	0	0	0	0	0	0	1	1
Malnutrition	0	0	0	0	0	0	0	1	0	0	1
Musculoskeletal and connective tissue disorders	1	2	0	5	14	12	7	2	2	0	45
Arthralgia	0	0	0	0	10	4	2	0	0	0	16
Arthritis	0	0	0	0	1	1	0	0	1	0	3
Back pain	0	1	0	1	1	2	2	0	0	0	7
Flank Pain	0	0	0	0	0	0	1	0	0	0	1
Generalized muscle weakness	0	0	0	0	0	1	0	0	0	0	1
Myalgia	0	0	0	1	0	2	1	0	0	0	4

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	0	1-30	31-60	61-180	181-365	366-730	731-1095	1096-1460	1461-1825	>1825	Total
Neck pain	0	1	0	0	0	0	1	0	0	0	2
Osteoporosis	0	0	0	0	0	0	0	0	1	0	1
Pain in extremity	1	0	0	2	2	1	0	1	0	0	7
Rhabdomyolysis	0	0	0	0	0	0	0	1	0	0	1
Superficial soft tissue fibrosis	0	0	0	1	0	1	0	0	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1	2	3	5	4	8	2	25
Acute Myeloid Leukemia	0	0	0	0	0	0	0	1	0	0	1
Benign Neoplasm	0	0	0	0	0	0	0	0	1	0	1
DCIS Left Breast	0	0	0	0	0	0	1	0	0	0	1
Diffuse Metastatic disease to the bones	0	0	0	0	0	0	0	1	0	0	1
Endometrial Cancer	0	0	0	0	0	0	2	0	0	0	2
Endometrial Cyst	0	0	0	0	0	1	0	0	0	0	1
Epidermal Inclusion Cyst	0	0	0	0	1	0	0	0	0	0	1
Hepatocellular carcinoma	0	0	0	0	0	0	0	1	0	0	1
Kidney cancer	0	0	0	0	0	0	0	0	1	0	1
Local recurrence	0	0	0	0	0	0	2	1	4	0	7
Lung Adenocarcinoma	0	0	0	0	1	0	0	0	0	0	1
Meningioma	0	0	0	1	0	0	0	0	0	0	1
Metastatic breast cancer	0	0	0	0	0	0	0	0	1	0	1
Mole	0	0	0	0	0	1	0	0	0	0	1
Non-small cell lung cancer	0	0	0	0	0	1	0	0	0	0	1
Second primary BC	0	0	0	0	0	0	0	0	1	2	3
Nervous system disorders	1	0	0	6	6	6	3	0	4	1	27
Altered mental status	0	0	0	0	0	0	0	0	1	0	1
Dizziness	0	0	0	0	1	2	0	0	0	1	4
Encephalopathy	0	0	0	0	1	0	0	0	0	0	1
Headache	0	0	0	1	2	0	0	0	0	0	3
Intracranial hemorrhage	0	0	0	1	0	0	0	0	0	0	1
Memory impairment	0	0	0	1	2	0	2	0	1	0	6
Paresthesia	1	0	0	1	0	0	0	0	0	0	2
Peripheral sensory neuropathy	0	0	0	1	0	0	0	0	0	0	1
Presyncope	0	0	0	0	0	0	1	0	0	0	1
Seizure	0	0	0	0	0	1	0	0	0	0	1
Spasticity	0	0	0	0	0	1	0	0	0	0	1
Stroke	0	0	0	1	0	0	0	0	1	0	2
Syncope	0	0	0	0	0	0	0	0	1	0	1
Thoracic stenosis	0	0	0	0	0	1	0	0	0	0	1
Transient ischemic attacks	0	0	0	0	0	1	0	0	0	0	1
Psychiatric disorders	2	0	0	1	8	3	0	0	0	0	14
Anxiety	1	0	0	0	4	1	0	0	0	0	6
Depression	0	0	0	0	2	1	0	0	0	0	3
Insomnia	0	0	0	1	2	1	0	0	0	0	4
Psychiatric disorders - Other Mild	1	0	0	0	0	0	0	0	0	0	1
Renal and urinary disorders	0	0	0	1	5	2	1	0	2	0	11
Acute kidney injury	0	0	0	0	2	0	0	0	2	0	4

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	0	1-30	31-60	61-180	181-365	366-730	731-1095	1096-1460	1461-1825	>1825	Total
Hematuria	0	0	0	0	1	0	0	0	0	0	1
Urinary frequency	0	0	0	0	1	1	0	0	0	0	2
Urinary incontinence	0	0	0	1	1	1	0	0	0	0	3
urinary tract pain	0	0	0	0	0	0	1	0	0	0	1
Reproductive system and breast disorders	0	1	0	0	4	0	0	0	1	0	6
Breast twitches	0	1	0	0	0	0	0	0	0	0	1
Dimpling	0	0	0	0	1	0	0	0	0	0	1
Dyspareunia	0	0	0	0	1	0	0	0	0	0	1
Tethering	0	0	0	0	1	0	0	0	0	0	1
Vaginal dryness	0	0	0	0	1	0	0	0	1	0	2
Respiratory, thoracic and mediastinal disorders	0	1	1	2	3	13	6	4	2	5	37
Aspiration	0	0	0	0	0	2	0	0	0	0	2
Atelectasis	0	0	0	0	0	0	0	0	1	0	1
COPD	0	0	0	0	0	1	0	0	0	1	2
Cough	0	0	0	0	2	3	1	0	0	0	6
Dyspnea	0	1	0	2	0	1	2	3	1	1	11
Emphysema	0	0	0	0	0	1	0	0	0	0	1
Hypoxia	0	0	0	0	0	2	0	0	0	0	2
Nasal congestion	0	0	0	0	0	1	0	0	0	0	1
Pleural effusion	0	0	0	0	0	1	2	1	0	2	6
Pulmonary edema	0	0	0	0	0	0	1	0	0	0	1
Respiratory failure	0	0	1	0	1	1	0	0	0	1	4
Skin and subcutaneous tissue disorders	2	11	0	2	4	1	0	0	1	0	21
Alopecia	0	0	0	0	1	0	0	0	0	0	1
Body odor	0	1	0	0	0	0	0	0	0	0	1
Drainage	0	1	0	0	0	0	0	0	0	0	1
Dry skin	0	0	0	0	1	0	0	0	0	0	1
Erythema multiforme	2	3	0	1	0	1	0	0	0	0	7
Hirsutism	0	0	0	0	1	0	0	0	0	0	1
Pruritus	0	4	0	1	0	0	0	0	1	0	6
Rash acneiform	0	1	0	0	0	0	0	0	0	0	1
Skin hyperpigmentation	0	0	0	0	1	0	0	0	0	0	1
Skin rash	0	1	0	0	0	0	0	0	0	0	1
Surgical and medical procedures	0	1	0	0	0	0	0	0	1	0	2
Hemiorrhaphy /Hemioplasty	0	0	0	0	0	0	0	0	1	0	1
Yellow discharge	0	1	0	0	0	0	0	0	0	0	1
Vascular disorders	8	3	0	4	5	2	4	1	0	0	27
Bilateral Carotid Stenosis	0	0	0	0	0	0	1	0	0	0	1
Flushing	1	0	0	0	0	0	0	0	0	0	1
Hematoma	7	2	0	0	0	0	0	0	0	0	9
Hot flashes	0	1	0	2	4	0	1	1	0	0	9
Hypertension	0	0	0	1	0	1	2	0	0	0	4
Thromboembolic event	0	0	0	1	1	1	0	0	0	0	3

Adverse events with missing date are analyzed as relative day 1.

Source: Tables Safety by Severity-Timecourse_FAS.sas; Analyzed: 09JUN2024

Briefing Document for the General and Plastic Surgery Devices Panel – **Appendix B**

A listing of all adverse events by AE code and severity can be seen below (**Table 1-4**). The majority of events were mild in severity.

Table 1-4: ICE3 Clinical Study All Adverse Events by AE Code and Severity - Primary Analysis Set (N=194)

	Mild		Moderate		Severe		Total Events
	Events	%*	Events	%*	Events	%*	
All Events	333	64.4%	92	17.8%	92	17.8%	517
Blood and lymphatic system disorders	1	14.3%	3	42.9%	3	42.9%	7
Anemia	0	0.0%	0	0.0%	1	100.0%	1
Febrile Neutropenia	0	0.0%	0	0.0%	2	100.0%	2
Leukocytosis	0	0.0%	2	100.0%	0	0.0%	2
Lymph node pain	1	50.0%	1	50.0%	0	0.0%	2
Cardiac disorders	6	26.1%	4	17.4%	13	56.5%	23
Acute coronary syndrome	1	100.0%	0	0.0%	0	0.0%	1
Aortic valve disease	0	0.0%	0	0.0%	1	100.0%	1
Atrial fibrillation	1	25.0%	2	50.0%	1	25.0%	4
Atrial flutter	1	100.0%	0	0.0%	0	0.0%	1
Atrioventricular Block Complete	0	0.0%	0	0.0%	1	100.0%	1
Cardiac arrest	0	0.0%	0	0.0%	2	100.0%	2
Chest pain - cardiac	0	0.0%	0	0.0%	2	100.0%	2
Heart failure	0	0.0%	2	40.0%	3	60.0%	5
Myocardial infarction	0	0.0%	0	0.0%	2	100.0%	2
Palpitations	3	100.0%	0	0.0%	0	0.0%	3
Sick sinus syndrome	0	0.0%	0	0.0%	1	100.0%	1
Ear and labyrinth disorders	3	60.0%	2	40.0%	0	0.0%	5
Ear Pain	0	0.0%	1	100.0%	0	0.0%	1
Hearing impaired	2	100.0%	0	0.0%	0	0.0%	2
Tinnitus	1	100.0%	0	0.0%	0	0.0%	1
Vestibular Disorder	0	0.0%	1	100.0%	0	0.0%	1
Eye disorders	1	50.0%	1	50.0%	0	0.0%	2
Cataract	1	100.0%	0	0.0%	0	0.0%	1
Macular degeneration	0	0.0%	1	100.0%	0	0.0%	1
Gastrointestinal disorders	10	43.5%	5	21.7%	8	34.8%	23
Abdominal Distension	1	100.0%	0	0.0%	0	0.0%	1
Abdominal pain	2	50.0%	1	25.0%	1	25.0%	4
Colitis	0	0.0%	0	0.0%	1	100.0%	1
Constipation	4	57.1%	1	14.3%	2	28.6%	7
Diarrhea	2	66.7%	0	0.0%	1	33.3%	3
Duodenal hemorrhage	0	0.0%	1	100.0%	0	0.0%	1
Dyspepsia	1	100.0%	0	0.0%	0	0.0%	1
Dysphagia	0	0.0%	0	0.0%	1	100.0%	1
Obstruction gastric	0	0.0%	0	0.0%	2	100.0%	2
Sigmoid diverticulitis	0	0.0%	1	100.0%	0	0.0%	1
Small intestinal obstruction	0	0.0%	1	100.0%	0	0.0%	1

Briefing Document for the General and Plastic Surgery Devices Panel – Appendix B

	Mild		Moderate		Severe		Total Events
	Events	%*	Events	%*	Events	%*	
General disorders and administration site conditions	111	88.8%	7	5.6%	7	5.6%	125
COVID	0	0.0%	1	33.3%	2	66.7%	3
Chills	1	100.0%	0	0.0%	0	0.0%	1
Death NOS	0	0.0%	0	0.0%	3	100.0%	3
Edema limbs	1	50.0%	0	0.0%	1	50.0%	2
Edema of limbs	0	0.0%	1	100.0%	0	0.0%	1
Fatigue	14	93.3%	1	6.7%	0	0.0%	15
Heat sensation	2	100.0%	0	0.0%	0	0.0%	2
Infusion site extravasation	1	100.0%	0	0.0%	0	0.0%	1
Injection site reaction	11	100.0%	0	0.0%	0	0.0%	11
Irritability	1	100.0%	0	0.0%	0	0.0%	1
Localized edema	35	92.1%	3	7.9%	0	0.0%	38
Malaise	1	100.0%	0	0.0%	0	0.0%	1
Multi-organ failure	0	0.0%	0	0.0%	1	100.0%	1
Non-cardiac chest pain	2	100.0%	0	0.0%	0	0.0%	2
Pain	42	97.7%	1	2.3%	0	0.0%	43
Infections and infestations	12	38.7%	9	29.0%	10	32.3%	31
Endocarditis infective	0	0.0%	0	0.0%	1	100.0%	1
Lung infection	2	33.3%	1	16.7%	3	50.0%	6
Papulopustular Rash	0	0.0%	1	100.0%	0	0.0%	1
Rash Pustular	1	100.0%	0	0.0%	0	0.0%	1
Sepsis	0	0.0%	0	0.0%	3	100.0%	3
Skin infection	8	53.3%	6	40.0%	1	6.7%	15
Upper respiratory infection	0	0.0%	1	100.0%	0	0.0%	1
Urinary tract infection	1	33.3%	0	0.0%	2	66.7%	3
Injury, poisoning and procedural complications	58	75.3%	14	18.2%	5	6.5%	77
Bruising	45	78.9%	9	15.8%	3	5.3%	57
Burn	2	50.0%	2	50.0%	0	0.0%	4
Dermatitis radiation	2	66.7%	1	33.3%	0	0.0%	3
Fall	6	75.0%	1	12.5%	1	12.5%	8
Fracture	2	66.7%	1	33.3%	0	0.0%	3
Hip fracture	0	0.0%	0	0.0%	1	100.0%	1
postoperative hemorrhage	1	100.0%	0	0.0%	0	0.0%	1
Investigations	2	50.0%	2	50.0%	0	0.0%	4
Cholesterol high	0	0.0%	1	100.0%	0	0.0%	1
Weight loss	2	66.7%	1	33.3%	0	0.0%	3
Metabolism and nutrition disorders	2	40.0%	1	20.0%	2	40.0%	5
Anorexia	1	100.0%	0	0.0%	0	0.0%	1
Hypercalcemia	0	0.0%	0	0.0%	1	100.0%	1
Hypertriglyceridemia	1	100.0%	0	0.0%	0	0.0%	1
Hypokalemia	0	0.0%	0	0.0%	1	100.0%	1
Malnutrition	0	0.0%	1	100.0%	0	0.0%	1
Musculoskeletal and connective tissue disorders	35	77.8%	9	20.0%	1	2.2%	45
Arthralgia	13	81.3%	3	18.8%	0	0.0%	16
Arthritis	1	33.3%	1	33.3%	1	33.3%	3

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	Mild		Moderate		Severe		Total Events
	Events	%*	Events	%*	Events	%*	
Back pain	6	85.7%	1	14.3%	0	0.0%	7
Flank Pain	1	100.0%	0	0.0%	0	0.0%	1
Generalized muscle weakness	1	100.0%	0	0.0%	0	0.0%	1
Myalgia	3	75.0%	1	25.0%	0	0.0%	4
Neck pain	2	100.0%	0	0.0%	0	0.0%	2
Osteoporosis	1	100.0%	0	0.0%	0	0.0%	1
Pain in extremity	6	85.7%	1	14.3%	0	0.0%	7
Rhabdomyolysis	1	100.0%	0	0.0%	0	0.0%	1
Superficial soft tissue fibrosis	0	0.0%	2	100.0%	0	0.0%	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	12.0%	12	48.0%	10	40.0%	25
Acute Myeloid Leukemia	0	0.0%	0	0.0%	1	100.0%	1
Benign Neoplasm	0	0.0%	1	100.0%	0	0.0%	1
DCIS Left Breast	0	0.0%	0	0.0%	1	100.0%	1
Diffuse Metastatic disease to the bones	0	0.0%	0	0.0%	1	100.0%	1
Endometrial Cancer	0	0.0%	1	50.0%	1	50.0%	2
Endometrial Cyst	1	100.0%	0	0.0%	0	0.0%	1
Epidermal Inclusion Cyst	1	100.0%	0	0.0%	0	0.0%	1
Hepatocellular carcinoma	0	0.0%	0	0.0%	1	100.0%	1
Kidney cancer	0	0.0%	0	0.0%	1	100.0%	1
Local recurrence	0	0.0%	7	100.0%	0	0.0%	7
Lung Adenocarcinoma	0	0.0%	1	100.0%	0	0.0%	1
Meningioma	0	0.0%	0	0.0%	1	100.0%	1
Metastatic breast cancer	0	0.0%	0	0.0%	1	100.0%	1
Mole	1	100.0%	0	0.0%	0	0.0%	1
Non-small cell lung cancer	0	0.0%	0	0.0%	1	100.0%	1
Second primary BC	0	0.0%	2	66.7%	1	33.3%	3
Nervous system disorders	12	44.4%	6	22.2%	9	33.3%	27
Altered mental status	0	0.0%	0	0.0%	1	100.0%	1
Dizziness	3	75.0%	1	25.0%	0	0.0%	4
Encephalopathy	0	0.0%	0	0.0%	1	100.0%	1
Headache	2	66.7%	1	33.3%	0	0.0%	3
Intracranial hemorrhage	0	0.0%	0	0.0%	1	100.0%	1
Memory impairment	4	66.7%	0	0.0%	2	33.3%	6
Paresthesia	1	50.0%	1	50.0%	0	0.0%	2
Peripheral sensory neuropathy	1	100.0%	0	0.0%	0	0.0%	1
Presyncope	0	0.0%	1	100.0%	0	0.0%	1
Seizure	0	0.0%	1	100.0%	0	0.0%	1
Spasticity	1	100.0%	0	0.0%	0	0.0%	1
Stroke	0	0.0%	1	50.0%	1	50.0%	2
Syncope	0	0.0%	0	0.0%	1	100.0%	1
Thoracic stenosis	0	0.0%	0	0.0%	1	100.0%	1
Transient ischemic attacks	0	0.0%	0	0.0%	1	100.0%	1
Psychiatric disorders	14	100.0%	0	0.0%	0	0.0%	14
Anxiety	6	100.0%	0	0.0%	0	0.0%	6
Depression	3	100.0%	0	0.0%	0	0.0%	3
Insomnia	4	100.0%	0	0.0%	0	0.0%	4
Psychiatric disorders - Other Mild	1	100.0%	0	0.0%	0	0.0%	1

Briefing Document for the General and Plastic Surgery Devices Panel – Appendix B

	Mild		Moderate		Severe		Total Events
	Events	%*	Events	%*	Events	%*	
Renal and urinary disorders	6	54.5%	2	18.2%	3	27.3%	11
Acute kidney injury	0	0.0%	1	25.0%	3	75.0%	4
Hematuria	1	100.0%	0	0.0%	0	0.0%	1
Urinary frequency	2	100.0%	0	0.0%	0	0.0%	2
Urinary incontinence	2	66.7%	1	33.3%	0	0.0%	3
urinary tract pain	1	100.0%	0	0.0%	0	0.0%	1
Reproductive system and breast disorders	6	100.0%	0	0.0%	0	0.0%	6
Breast twitches	1	100.0%	0	0.0%	0	0.0%	1
Dimpling	1	100.0%	0	0.0%	0	0.0%	1
Dyspareunia	1	100.0%	0	0.0%	0	0.0%	1
Tethering	1	100.0%	0	0.0%	0	0.0%	1
Vaginal dryness	2	100.0%	0	0.0%	0	0.0%	2
Respiratory, thoracic and mediastinal disorders	14	37.8%	7	18.9%	16	43.2%	37
Aspiration	1	50.0%	0	0.0%	1	50.0%	2
Atelectasis	1	100.0%	0	0.0%	0	0.0%	1
COPD	1	50.0%	0	0.0%	1	50.0%	2
Cough	6	100.0%	0	0.0%	0	0.0%	6
Dyspnea	4	36.4%	2	18.2%	5	45.5%	11
Emphysema	0	0.0%	0	0.0%	1	100.0%	1
Hypoxia	0	0.0%	1	50.0%	1	50.0%	2
Nasal congestion	1	100.0%	0	0.0%	0	0.0%	1
Pleural effusion	0	0.0%	4	66.7%	2	33.3%	6
Pulmonary edema	0	0.0%	0	0.0%	1	100.0%	1
Respiratory failure	0	0.0%	0	0.0%	4	100.0%	4
Skin and subcutaneous tissue disorders	18	85.7%	3	14.3%	0	0.0%	21
Alopecia	1	100.0%	0	0.0%	0	0.0%	1
Body odor	1	100.0%	0	0.0%	0	0.0%	1
Drainage	1	100.0%	0	0.0%	0	0.0%	1
Dry skin	1	100.0%	0	0.0%	0	0.0%	1
Erythema multiforme	5	71.4%	2	28.6%	0	0.0%	7
Hirsutism	1	100.0%	0	0.0%	0	0.0%	1
Pruritus	6	100.0%	0	0.0%	0	0.0%	6
Rash acneiform	1	100.0%	0	0.0%	0	0.0%	1
Skin hyperpigmentation	0	0.0%	1	100.0%	0	0.0%	1
Skin rash	1	100.0%	0	0.0%	0	0.0%	1
Surgical and medical procedures	1	50.0%	1	50.0%	0	0.0%	2
Hemiorrhaphy /Hemioplasty	0	0.0%	1	100.0%	0	0.0%	1
Yellow discharge	1	100.0%	0	0.0%	0	0.0%	1
Vascular disorders	18	66.7%	4	14.8%	5	18.5%	27
Bilateral Carotid Stenosis	0	0.0%	1	100.0%	0	0.0%	1
Flushing	1	100.0%	0	0.0%	0	0.0%	1
Hematoma	8	88.9%	1	11.1%	0	0.0%	9
Hot flashes	8	88.9%	0	0.0%	1	11.1%	9
Hypertension	1	25.0%	1	25.0%	2	50.0%	4
Thromboembolic event	0	0.0%	1	33.3%	2	66.7%	3

	Mild		Moderate		Severe		Total
	Events	%*	Events	%*	Events	%*	Events
*Percentage of total events.							
Source: Tables Safety by Severity-Timecourse_FAS.sas; Analyzed: 09JUN2024							

1.2. Procedure Related Adverse Events

The procedure related adverse events are summarized in **Table 1-5**. In total, 180 procedure-related events were reported by 93 patients. The most prevalent procedure-related events were localized edema, bruising and pain. All adverse events are anticipated and accounted for in ProSense™ labeling; use of ProSense™ for the treatment of breast cancer does not introduce any new risks.

Table 1-5: ICE3 Clinical Study All Procedure Related Adverse Events – Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
All Events	180	93	47.9%
General disorders and administration site conditions	91	67	34.5%
Fatigue	2	2	1.0%
Heat sensation	1	1	0.5%
Infusion site extravasation	1	1	0.5%
Injection site reaction	11	10	5.2%
Localized edema	37	36	18.6%
Non-cardiac chest pain	1	1	0.5%
Pain	38	36	18.6%
Injury, poisoning and procedural complications	62	59	30.4%
Bruising	57	57	29.4%
Burn	4	4	2.1%
postoperative hemorrhage	1	1	0.5%
Musculoskeletal and connective tissue disorders	1	1	0.5%
Pain in extremity	1	1	0.5%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	3	1.5%
Local recurrence	3	3	1.5%
Metastatic breast cancer	1	1	0.5%
Reproductive system and breast disorders	3	2	1.0%
Breast twitches	1	1	0.5%
Dimpling	1	1	0.5%
Tethering	1	1	0.5%
Skin and subcutaneous tissue disorders	8	8	4.1%
Drainage	1	1	0.5%
Erythema multiforme	3	3	1.5%
Pruritus	3	3	1.5%
Rash acneiform	1	1	0.5%
Surgical and medical procedures	1	1	0.5%
Yellow discharge	1	1	0.5%
Vascular disorders	10	10	5.2%
Flushing	1	1	0.5%
Hematoma	9	9	4.6%

† Total number of events without regard to length of follow-up.

‡ Number of subjects experiencing event without regard to length of follow-up.

° Percentage of subjects experiencing specific event without regard to length of follow-up.

Procedure relationship: Remotely, Possible, Probable, Unknown.

Adverse events with missing date are analyzed as relative day 1.

Source: Tables Safety_FAS.sas; Analyzed: 09JUN2024

The timecourse of procedure-related adverse events in the Primary Analysis Set are shown below in **Table 1-6**. A majority of events occurred within 1 month of surgery with many reported on the day of the procedure.

Table 1-6: ICE3 Clinical Study All Procedure Related Adverse Events by AE Code and Timecourse - Primary Analysis Set (N=194)

	Days Post-Op											
	Missing	0	1-30	31-60	61-180	181-365	366-730	731-1095	1096-1460	1461-1825	>1825	Total
All Events	0	62	102	1	1	6	3	2	1	2	0	180
General disorders and administration site conditions	0	34	47	1	1	4	3	0	1	0	0	91
Fatigue	0	1	1	0	0	0	0	0	0	0	0	2
Heat sensation	0	0	0	0	0	0	1	0	0	0	0	1
Infusion site extravasation	0	0	1	0	0	0	0	0	0	0	0	1
Injection site reaction	0	3	6	0	0	0	2	0	0	0	0	11
Localized edema	0	11	24	0	1	1	0	0	0	0	0	37
Non-cardiac chest pain	0	1	0	0	0	0	0	0	0	0	0	1
Pain	0	18	15	1	0	3	0	0	1	0	0	38
Injury, poisoning and procedural complications	0	18	44	0	0	0	0	0	0	0	0	62
Bruising	0	16	41	0	0	0	0	0	0	0	0	57
Burn	0	1	3	0	0	0	0	0	0	0	0	4
postoperative hemorrhage	0	1	0	0	0	0	0	0	0	0	0	1
Musculoskeletal and connective tissue disorders	0	1	0	0	0	0	0	0	0	0	0	1
Pain in extremity	0	1	0	0	0	0	0	0	0	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	0	2	0	2	0	4
Local recurrence	0	0	0	0	0	0	0	2	0	1	0	3
Metastatic breast cancer	0	0	0	0	0	0	0	0	0	1	0	1
Reproductive system and breast disorders	0	0	1	0	0	2	0	0	0	0	0	3
Breast twitches	0	0	1	0	0	0	0	0	0	0	0	1
Dimpling	0	0	0	0	0	1	0	0	0	0	0	1
Tethering	0	0	0	0	0	1	0	0	0	0	0	1
Skin and subcutaneous tissue disorders	0	1	7	0	0	0	0	0	0	0	0	8
Drainage	0	0	1	0	0	0	0	0	0	0	0	1
Erythema multiforme	0	1	2	0	0	0	0	0	0	0	0	3
Pruritus	0	0	3	0	0	0	0	0	0	0	0	3
Rash acneiform	0	0	1	0	0	0	0	0	0	0	0	1
Surgical and medical procedures	0	0	1	0	0	0	0	0	0	0	0	1
Yellow discharge	0	0	1	0	0	0	0	0	0	0	0	1
Vascular disorders	0	8	2	0	0	0	0	0	0	0	0	10
Flushing	0	1	0	0	0	0	0	0	0	0	0	1
Hematoma	0	7	2	0	0	0	0	0	0	0	0	9

†Defined as Remotely/Possible/Probable and Unknown.
Adverse events with missing date are analyzed as relative day 1.
Source: Tables Safety by Severity-Timecourse_FAS.sas; Analyzed: 09JUN2024

Procedure related adverse events stratified by AE code and severity in the Primary Analysis Set are shown below in **Table 1-7**. A majority of procedure-related events were mild in severity. None

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of the procedure-related adverse events were classified as ‘serious’. All adverse events were resolved without residual effects.

Table 1-7: ICE3 Clinical Study All Procedure Related Adverse Events by AE Code and Severity - Primary Analysis Set (N=194)

	Mild		Moderate		Severe		Total Events
	Events	%*	Events	%*	Events	%*	
All Events	158	87.8%	18	10.0%	4	2.2%	180
General disorders and administration site conditions	88	96.7%	3	3.3%	0	0.0%	91
Fatigue	2	100.0%	0	0.0%	0	0.0%	2
Heat sensation	1	100.0%	0	0.0%	0	0.0%	1
Infusion site extravasation	1	100.0%	0	0.0%	0	0.0%	1
Injection site reaction	11	100.0%	0	0.0%	0	0.0%	11
Localized edema	35	94.6%	2	5.4%	0	0.0%	37
Non-cardiac chest pain	1	100.0%	0	0.0%	0	0.0%	1
Pain	37	97.4%	1	2.6%	0	0.0%	38
Injury, poisoning and procedural complications	48	77.4%	11	17.7%	3	4.8%	62
Bruising	45	78.9%	9	15.8%	3	5.3%	57
Burn	2	50.0%	2	50.0%	0	0.0%	4
postoperative hemorrhage	1	100.0%	0	0.0%	0	0.0%	1
Musculoskeletal and connective tissue disorders	1	100.0%	0	0.0%	0	0.0%	1
Pain in extremity	1	100.0%	0	0.0%	0	0.0%	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.0%	3	75.0%	1	25.0%	4
Local recurrence	0	0.0%	3	100.0%	0	0.0%	3
Metastatic breast cancer	0	0.0%	0	0.0%	1	100.0%	1
Reproductive system and breast disorders	3	100.0%	0	0.0%	0	0.0%	3
Breast tw itches	1	100.0%	0	0.0%	0	0.0%	1
Dimpling	1	100.0%	0	0.0%	0	0.0%	1
Tethering	1	100.0%	0	0.0%	0	0.0%	1
Skin and subcutaneous tissue disorders	8	100.0%	0	0.0%	0	0.0%	8
Drainage	1	100.0%	0	0.0%	0	0.0%	1
Erythema multiforme	3	100.0%	0	0.0%	0	0.0%	3
Pruritus	3	100.0%	0	0.0%	0	0.0%	3
Rash acneiform	1	100.0%	0	0.0%	0	0.0%	1
Surgical and medical procedures	1	100.0%	0	0.0%	0	0.0%	1
Yellow discharge	1	100.0%	0	0.0%	0	0.0%	1
Vascular disorders	9	90.0%	1	10.0%	0	0.0%	10
Flushing	1	100.0%	0	0.0%	0	0.0%	1
Hematoma	8	88.9%	1	11.1%	0	0.0%	9

*Percentage of total events. †Defined as Remotely/Possible/Probable and Unknow n.

Source: Tables Safety by Severity-Timecourse_FAS.sas; Analyzed: 09JUN2024

1.3. Serious Adverse Events

Serious adverse events are summarized in **Table 1-8**. In total, 127 serious adverse events were recorded by 59 patients. Per FDA request, all cases of breast cancer recurrence (local and distant) as well as second primary breast cancer are reported as serious adverse events (13 events in 12 patients). The study device relationship was classified by DSMB review. Four (4) serious adverse events were classified as possibly related to the procedure; all other SAEs were due to comorbidities or factors other than cryoablation treatment for breast cancer.

Table 1-8: ICE3 Clinical Study All Serious Adverse Events by High and Low Terms - Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
All Events	127	59	30.4%
Blood and lymphatic system disorders	4	4	2.1%
Anemia	1	1	0.5%
Febrile Neutropenia	2	2	1.0%
Leukocytosis	1	1	0.5%
Cardiac disorders	18	13	6.7%
Acute coronary syndrome	1	1	0.5%
Aortic valve disease	1	1	0.5%
Atrial fibrillation	2	2	1.0%
Atrioventricular Block Complete	1	1	0.5%
Cardiac arrest	2	2	1.0%
Chest pain - cardiac	2	1	0.5%
Heart failure	5	4	2.1%
Myocardial infarction	2	2	1.0%
Palpitations	1	1	0.5%
Sick sinus syndrome	1	1	0.5%
Ear and labyrinth disorders	1	1	0.5%
Vestibular Disorder	1	1	0.5%
Gastrointestinal disorders	10	9	4.6%
Abdominal pain	1	1	0.5%
Colitis	1	1	0.5%
Constipation	2	2	1.0%
Duodenal hemorrhage	1	1	0.5%
Dysphagia	1	1	0.5%
Obstruction gastric	2	1	0.5%
Sigmoid diverticulitis	1	1	0.5%
Small intestinal obstruction	1	1	0.5%
General disorders and administration site conditions	8	6	3.1%
COVID	3	2	1.0%
Death NOS	3	3	1.5%
Edema limbs	1	1	0.5%
Multi-organ failure	1	1	0.5%
Infections and infestations	16	13	6.7%
Endocarditis infective	1	1	0.5%
Lung infection	5	5	2.6%
Sepsis	3	3	1.5%
Skin infection	4	3	1.5%
Upper respiratory infection	1	1	0.5%
Urinary tract infection	2	2	1.0%
Injury, poisoning and procedural complications	4	4	2.1%
Fall	2	2	1.0%
Fracture	1	1	0.5%
Hip fracture	1	1	0.5%

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	ICECURE (N= 194)		
	Events†	Subjs‡	%°
Metabolism and nutrition disorders	3	3	1.5%
Hypercalcemia	1	1	0.5%
Hypokalemia	1	1	0.5%
Malnutrition	1	1	0.5%
Musculoskeletal and connective tissue disorders	2	2	1.0%
Arthritis	1	1	0.5%
Rhabdomyolysis	1	1	0.5%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21	20	10.3%
Acute Myeloid Leukemia	1	1	0.5%
DCIS Left Breast	1	1	0.5%
Diffuse Metastatic disease to the bones	1	1	0.5%
Endometrial Cancer	2	2	1.0%
Hepatocellular carcinoma	1	1	0.5%
Kidney cancer	1	1	0.5%
Local recurrence	7	7	3.6%
Lung Adenocarcinoma	1	1	0.5%
Meningioma	1	1	0.5%
Metastatic breast cancer	1	1	0.5%
Non-small cell lung cancer	1	1	0.5%
Second primary BC	3	3	1.5%
Nervous system disorders	12	12	6.2%
Altered mental status	1	1	0.5%
Encephalopathy	1	1	0.5%
Intracranial hemorrhage	1	1	0.5%
Memory impairment	3	3	1.5%
Presyncope	1	1	0.5%
Stroke	2	2	1.0%
Syncope	1	1	0.5%
Thoracic stenosis	1	1	0.5%
Transient ischemic attacks	1	1	0.5%
Renal and urinary disorders	4	4	2.1%
Acute kidney injury	4	4	2.1%
Respiratory, thoracic and mediastinal disorders	18	12	6.2%
Aspiration	1	1	0.5%
COPD	1	1	0.5%
Dyspnea	5	2	1.0%
Emphysema	1	1	0.5%
Hypoxia	1	1	0.5%
Pleural effusion	4	4	2.1%
Pulmonary edema	1	1	0.5%
Respiratory failure	4	4	2.1%
Vascular disorders	6	5	2.6%
Bilateral Carotid Stenosis	1	1	0.5%
Hypertension	2	2	1.0%
Thromboembolic event	3	3	1.5%

† Total number of events without regard to length of follow-up.

‡ Number of subjects experiencing event without regard to length of follow-up.

° Percentage of subjects experiencing specific event without regard to length of follow-up.

Procedure relationship: Remotely, Possible, Probable, Unknown.

Adverse events with missing date are analyzed as relative day 1.

Source: Tables Safety_FAS.sas; Analyzed: 09JUN2024

1.4. Serious Procedure Related Adverse Events

Among the Primary Analysis Set, the DSMB conservatively classified a total of four (4) serious adverse events in three (3) patients to be possibly related to the study procedure/device, due to inadequate treatment. One (1) patient (b) (6) due to probe mispositioning during cryoablation, and two (2) patients [REDACTED] and (b) (6) due to violation of specified treatment procedures in the clinical study protocol. (b) (6) had both local recurrence and distant recurrence; this patient was reviewed by the DSMB retrospectively and believed not to be eligible based on MammaPrint results, which suggested Luminal B pathology. All four events occurred greater than 2-years post-op. The DSMB classified three of the events as moderate in severity and one as severe.

All four serious procedure-related events occurred after more than 2 years post-cryoablation. Two (2) serious, procedure related adverse events resolved without residual effect, and the remaining two serious, procedure related adverse events resulted in treatment of local recurrence and death due to metastatic disease.

Table 1-9: ICE3 Clinical Study All Serious Procedure Related Adverse Events by High and Low Terms - Primary Analysis Set (N=194)

	ICECURE (N= 194)		
	Events†	Subjs‡	%°
All Events	4	3	1.5%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	3	1.5%
Local recurrence	3	3	1.5%
Metastatic breast cancer	1	1	0.5%
† Total number of events without regard to length of follow-up. ‡ Number of subjects experiencing event without regard to length of follow-up. ° Percentage of subjects experiencing specific event without regard to length of follow-up. Procedure relationship: Remotely, Possible, Probable, Unknown. Adverse events with missing date are analyzed as relative day 1. Source: Tables Safety_FAS.sas; Analyzed: 09JUN2024			