SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Fluorescence imaging for breast cancer detection
Device Trade Name:	Lumicell Direct Visualization System (DVS)
Device Procode:	SAW
Applicant's Name and Address:	Lumicell, Inc. 275 Washington Street, Suite 200 Newton, MA 02458
Date(s) of Panel Recommendation:	N/A

Premarket Approval Application (PMA) Number: P230014

Date of FDA Notice of Approval: April 17, 2024

Breakthrough Device: Granted breakthrough device status on March 28, 2018, because the device meets the Breakthrough criteria. The Lumicell DVS is indicated for use in patients undergoing a breast conserving surgery (lumpectomy) to remove breast cancer. The Lumicell DVS is intended to be used whenever breast tissue is removed, histopathology evaluation of the tissue is the standard of care and/or it is essential that the tissue margins be examined for completeness of removal using standard surgical procedures. The Lumicell DVS is to be used in vivo following the excision of the main lumpectomy specimen to assist in locating residual abnormal tissue.

II. INDICATIONS FOR USE

The combination product consists of an optical imaging agent, LUMISIGHT (pegulicianine) for injection (NDA 214511), and a fluorescence imaging device, the Lumicell Direct Visualization System (DVS). The Lumicell Direct Visualization System is intended for use in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

The Lumicell DVS is used with LUMISIGHT for fluorescence imaging of the lumpectomy cavity.

LUMISIGHT Indications for Use: LUMISIGHT is an optical imaging agent indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of

cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

III. CONTRAINDICATIONS

There are no known contraindications for the Lumicell DVS. LUMISIGHT is contraindicated in patients with a history of hypersensitivity reaction to pegulicianine. Reactions have included anaphylaxis. Refer to LUMISIGHT's Prescribing Information for full safety information.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions for the Lumicell DVS can be found in the Lumicell DVS Instructions for Use. The warnings and precautions for LUMISIGHT (pegulicianine) for injection can be found in the LUMISIGHT Prescribing Information (PI) (refer to NDA 214511, and Appendix I).

V. DEVICE DESCRIPTION

LUMISIGHT and Lumicell Direct Visualization System is a combination product indicated as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery and consists of:

- Device constituent: Lumicell Direct Visualization System (DVS) fluorescence imaging device
- Drug constituent: LUMISIGHT (pegulicianine) for injection optical imaging agent

LUMISIGHT is provided as a sterile, dark blue lyophilized powder in a clear vial which contains 40 mg of pegulicianine, 39.5 mg of mannitol, 3.8 mg of monobasic sodium phosphate monohydrate and 3.2 mg of dibasic sodium phosphate heptahydrate. Please refer to the LUMISIGHT Prescribing Information for details.

The Lumicell Direct Visualization System (DVS) consists of a Workstation and a Handheld Probe (Figure 1). The Handheld Probe connects to the Workstation's Light Source via an optical fiber cable. These components are used together to excite the optical imaging agent, LUMISIGHT, and capture and display real-time fluorescence images. During surgery, the Handheld Probe is used to scan the lumpectomy cavity for activated LUMISIGHT by delivering 630 ± 5 nm excitation light and measuring the fluorescence emission signal using a camera after filtering through a 662.5 – 737.5 nm bandpass filter. The resulting data is transferred to the Workstation's Touchscreen via USB cable. The data is analyzed in real-time via Lumicell's proprietary Patient Calibrated Tumor Detection Software to highlight regions within the lumpectomy cavity that are suspicious of containing residual cancer.

The Lumicell DVS will be packaged and sold separately from LUMISIGHT. Each will be co-labeled with instructions for the use of the drug and device constituents to combination usage.

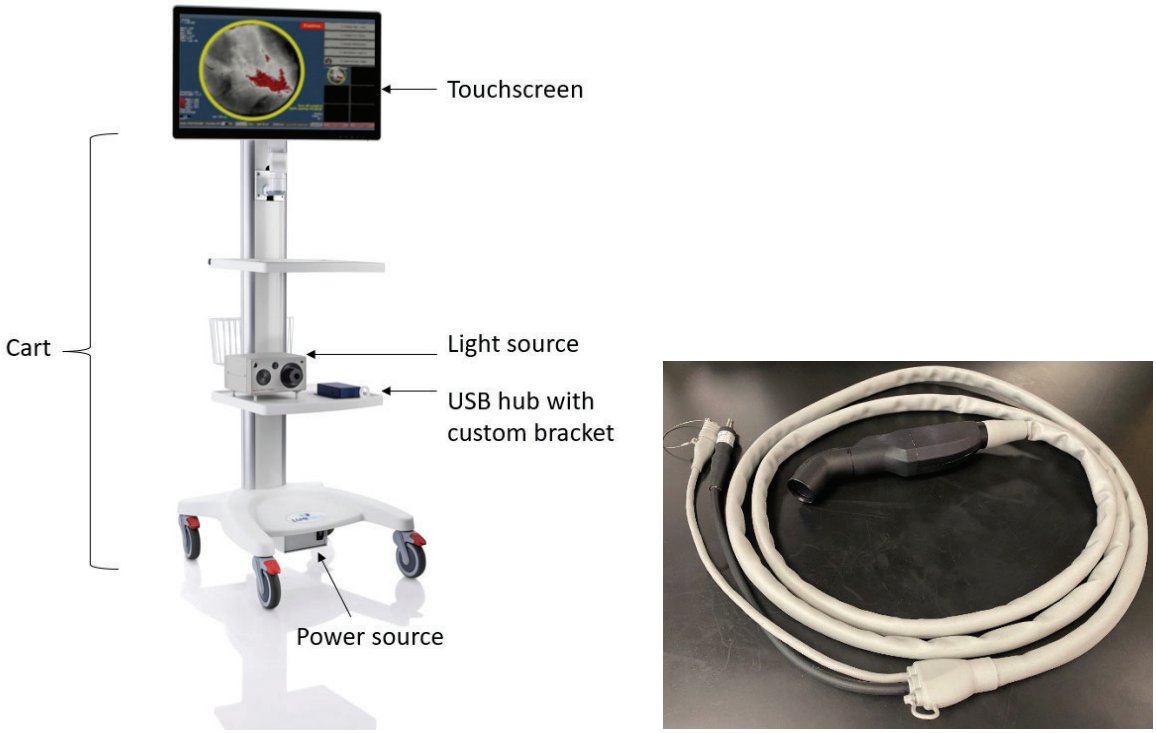


Figure 1. Lumicell Direct Visualization System (DVS). Left: Workstation, right: Handheld Probe with cables

A. Changes Between the Clinical and Commercial Product

There were some changes implemented to the Lumicell DVS between the pivotal study and commercial versions. The changes were primarily for manufacturability, usability, and sterilizability of the hand-held probe. There were no changes to the device principles of operation or performance. Key device changes are noted in Table 1 below.

Table 1. Key Changes between Clinical Study Device and Commercial Device

Probe and Cable	Enclosure improved, no changes to optics or performance
Sterile Cover	Added second layer, changed to rolled configuration with applicator
Computer	Changed to medical grade all-in-one touchscreen computer
Software	Improved user interface, no change to image analysis algorithm

Results from system-level equivalence testing show that all key performance parameters were within specification. Equivalency testing included fluorescence detection sensitivity, signal linearity, field of view, magnification, distortion, spatial resolution, depth of field, signal uniformity, and excitation light crosstalk. All results met prespecified acceptance criteria and it was concluded that optical performance between the clinical study and commercial versions of the Lumicell DVS were equivalent.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Currently, no FDA-approved intraoperative technology is available that directly examines the lumpectomy cavity for residual cancer after the main specimen is removed in Breast-Conserving Surgery (BCS; partial removal of breast tissue or lumpectomy). Moreover, no *in-vivo* imaging products or modalities are available to assist breast cancer surgeons in examining the lumpectomy cavity for a signal of residual cancer, which would facilitate excision of cancer that remains *in-situ* during and after the initial surgery. One available technology uses radiofrequency spectroscopy intraoperatively, but it is used to examine the excised specimen, which can present challenges translating the suspected location containing cancer from the excised specimen to the corresponding location within the cavity. There are multiple alternative intraoperative breast cancer diagnosis options, including specimen X-ray, intraoperative sonography, etc. There are several non-intraoperative alternatives for breast cancer diagnosis, including clinical breast examination, mammography, color and power Doppler, strain and shear wave elastography, magnetic resonance imaging, and molecular breast imaging. There is an alternative breast cancer surgical intervention - removal of the entire breast (mastectomy). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

LUMISIGHT and Lumicell DVS have not previously been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE COMBINATION PRODUCT ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of LUMISIGHT and the Lumicell DVS.

Serious hypersensitivity reactions, including anaphylaxis, have been reported following administration of LUMISIGHT (see the Boxed Warning and the Warnings and Precautions in the LUMISIGHT Prescribing Information in the Appendix).

Adverse reactions occurring in ≥ 1% of patients receiving LUMISIGHT were hypersensitivity (1.4%, including anaphylaxis [4 out of 726]) and chromaturia 85%). Chromaturia resolved within 48 hours after administration in 93% of patients, with the longest time to resolution of 15 days.

Adverse reactions occurring in < 1% of patients were skin discoloration after extravasation, nausea, dyspnea, pyrexia, and vomiting.

Patients should be informed that if extravasation of LUMISIGHT occurs, it may result in blue discoloration of the skin at the injection site that will be evident for several weeks.

No serious adverse device effects have been observed to date in any of the clinical trials using the Lumicell DVS. While not related to the Lumicell DVS, common surgical-related adverse events are anticipated. These may include but are not limited to surgery site infection, seroma, hematoma, and delayed wound healing. These events are anticipated to occur at an equivalent rate to standard of care surgery.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. System Level Testing

System level testing was done for: hardware safety, electromagnetic compatibility (EMC), software and hardware verification & validation, cleaning, packaging and shipping validation, usability, performance equivalency between clinical and commercial systems, and biocompatibility. Testing for the system ensured that the Lumicell DVS met established specifications for the planned commercial product. These tests are summarized in Table 2.

Table 2: Summary of system-level testing

Test	Purpose	Method	Result
Hardware Safety Test	Test basic safety and essential performance of medical electrical equipment with endoscopic functionality and a light source	According to ANSI AAMI ES60601-1:2005/(R)2012 & A1:2012, C1:2009/(R)2012 & A2:2010/(R)2012 (Cons. Text) Medical electrical equipment - Part 1: General requirements for basic safety and essential performance IEC 60601-2-18 Ed. 3.0 b:2009 Medical electrical equipment - Part 2-18: Particular requirements for the basic safety and essential performance of endoscopic equipment IEC 60601-2-57 Ed. 1.0 b:2011 Medical electrical equipment - Part 2-57: Particular requirements for the basic safety and essential performance of non-laser light source equipment intended for therapeutic, diagnostic, monitoring and cosmetic/aesthetic use	Passed
EMC Test	Test for Electromagnetic Compatibility	IEC 60601-1-2 Ed. 4.1 b:2020 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests, and related standards	Passed

Test	Purpose	Method	Result
Software Verification & Validation	Test software unit and system level performance and accuracy, and ensure cybersecurity	IEC 62304 Ed. 1.1 b:2015 General Principles of Software Validation Guidance for Industry and Food and Drug Administration Staff (January 11, 2002) Off-The-Shelf Software Use in Medical Devices Guidance for Industry and Food and Drug Administration Staff (September 27, 2019) Content of Premarket Submissions for Management of Cybersecurity in Medical Devices Guidance for Industry and Food and Drug Administration Staff (October 2, 2014) Guidance for Industry and Food and Drug Administration Staff (October 2, 2014)	Passed
Hardware Verification	Ensure system meets requirements	Verification tests were conducted on the system's hardware to verify that system meets design requirements	Passed
Cleaning- Imaging Station	Test cleanability of Imaging Station	Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff (March 17, 2015) Guidance for Industry and Food and Drug Administration Staff (March 17, 2015) AAMI TIR30:2011/(R)2016 A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices	Passed
Packaging and Shipping-Imaging Station	Test that packaging configuration maintains the integrity of the package and product during handling and transportation.	ASTM D4169-22 Standard Practice for Performance Testing of Shipping Containers and Systems ASTM F2825-18: Climatic Stressing of Packaging Systems for Single Parcel Delivery	Passed
Usability	Test usability of system	Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff (February 3, 2016) IEC 62366-1 Ed. 1.1 b:2020 Medical devices - Part 1: Application of usability engineering to medical devices	Passed
System Equivalence	To ensure that the optical performance of the Clinical and Commercial versions perform the same	Tests for sensitivity, signal linearity, field of view, magnification, distortion, spatial resolution, depth of field, signal uniformity, and excitation light crosstalk must meet prespecified acceptance criteria	Passed

Test	Purpose	Method	Result
Software Equivalence	To ensure that the Clinical and Commercial software versions perform the same	Pivotal study images analyzed by both versions should have same results	Passed
Biocompatibility-Lumicell DVS	Assess biocompatibility at the system level	Use of International Standard ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff (September 4, 2020) ISO 10993-1:2018 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	Passed

B. Component Testing

Component testing included biocompatibility, sterilization, reusability, packaging, and shipping for various components of the Lumicell DVS. Testing for components ensured that they met established specifications for the planned commercial product. These tests are summarized in Table 3.

Table 3: Summary of component testing

Test	Purpose	Method	Result
Biocompatibility-Sterile Cover	Test biocompatibility	Use of International Standard ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff (September 4, 2020) ISO 10993-1:2018 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process ISO 10993-5:2009 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity ISO 10993-10:2021 Biological evaluation of medical devices - Part 10: Tests for skin sensitization ISO 10993-11:2017 Biological evaluation of medical devices - Part 11: Tests for systemic toxicity ISO 10993-12:2012 Biological evaluation of medical devices - Part 12: Sample Preparation	Passed

Test	Purpose	Method	Result
Sterilization-Sterile Cover and Calibration Plate	Validation of sterilization process	ISO 11135:2014+A1:2019 Sterilization of health-care products-Ethylene oxide-Requirements for the development, validation and routine control of a sterilization process for medical devices ISO 10993-7:2008 Biological Evaluation of medical devices- Part 7: Ethylene oxide residuals	Passed
Packaging, Shipping, and Shelf Life-Sterile Cover and Calibration Plate	Test that packaging configuration maintains the sterility of the product, and integrity of the package and product during handling and transportation over its shelf life	ISO 11607-1:2019 Packaging for Terminally Sterilized Devices, Parts 1 and 2 ASTM D4332-14 Standard Practice for Conditioning Containers, Packages, or Packaging Components ASTM F1886-16 Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection ASTM F2096-19 Standard Test Method For Detecting Gross Leaks In Medical Packaging By Internal Pressurization (Bubble Test)	Passed
Cleaning-Handheld Probe and Sterilization Tray	Validate cleaning instructions for Handheld Probe and Sterilization Tray	Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff (March 17, 2015) AAMI TIR30:2011/(R)2016 (Handheld Probe) ANSI/AAMI ST98:2022 (Sterilization Tray) A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices	Passed
Sterilization-Handheld Probe and Sterilization Tray	Validate sterilization instructions for Handheld Probe and Sterilization Tray	ISO 14937 (2009): Sterilization of Health Care Products – General Requirements for Characterization of a Sterilizing Agent and the Development, Validation and Routine Control of a Sterilization Process for Medical Devices 7.2 AAMI TIR No. 12-2020: Designing, Testing, and Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: A Guide for Medical Device Manufacturers	Passed
Reuse-Handheld Probe	Test failures of reuse to inform labeling	Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff (March 17, 2015) ISO 17664-1:2021 Processing of health care products - Information to be provided by the medical device	Passed

Test	Purpose	Method	Result
		manufacturer for the processing of medical devices – Parts 1 and 2	
Packaging and Shipping- Handheld Probe	Test that packaging configuration maintains the integrity of the package and product during handling and transportation.	ASTM D4169-16 Standard Practice for Performance Testing of Shipping Containers and Systems ASTM F2825-18: Climatic Stressing of Packaging Systems for Single Parcel Delivery	Passed
Packaging and Shipping- Light Source	Test that packaging configuration maintains the integrity of the package and product during handling and transportation.	ASTM D4169-16 Standard Practice for Performance Testing of Shipping Containers and Systems ASTM F2825-18: Climatic Stressing of Packaging Systems for Single Parcel Delivery	Passed

C. Animal Studies

Early in the development of LUMISIGHT and the Lumicell DVS, animal studies were conducted. These studies are summarized in Table 4.

Table 4: Summary of animal studies

Study	Purpose	Result
Proof-of-Concept Studies in Mouse Models for Cancer	Studied LUMISIGHT labeling of tumors	Demonstrated residual fluorescence within tumor bed
Proof-of-Concept Studies in Dog Patients	Studied LUMISIGHT with prototype Lumicell DVS for imaging in dogs with cancer	Correctly distinguished cancer from normal tissue in 92% of biopsies

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The Applicant performed a pivotal clinical study (CL0007) in the US to establish a reasonable assurance of safety and effectiveness of LUMISIGHT and Lumicell DVS for use in patients with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery (NCT03686215). Data from this pivotal/PMA clinical study is presented below.

Additionally, a multicenter feasibility study was conducted (termed Phase C Study or CL0006) and is included as a supporting study for the evaluation of safety and effectiveness of LUMISIGHT and the Lumicell DVS (IDE G140195, NCT03321929).

Safety evaluations of LUMISIGHT for these two studies are presented in Section X.D.1 and XI.1, respectively. An overall safety assessment was also conducted in all breast cancer patients and all cancer patients treated across multiple indications from other ongoing and completed clinical studies and is presented in Section XI.2. The safety information of the drug use is analyzed based on all the patients in these trials.

Pivotal Study (CL0007)

A. Study Design

Patients were enrolled between 04 November 2019 and 15 September 2021. The database for this PMA reflected data collected through 15 September 2021 and included 406 patients. There were 14 investigational sites in the United States.

The Pivotal Study was a multicenter, two-arm, randomized, study designed to demonstrate the safety and effectiveness of LUMISIGHT and the Lumicell DVS in identifying residual cancer in the lumpectomy cavity of female patients with breast cancer. Eligible patients consented to participate in the study with histologically or cytologically confirmed primary invasive breast cancer, ductal carcinoma in situ (DCIS), or primary invasive breast cancer with a DCIS component.

Prior to randomization, all patients were injected with LUMISIGHT at a dose of 1 mg/kg 2-6 hours prior to the recording of any image. Upon completion of the standard of care (SoC) BCS, it was revealed whether the patient was randomized into the treatment arm or the control arm. In the treatment arm, the surgeon used the Lumicell DVS to scan the lumpectomy cavity to identify and remove regions suspicious of containing residual cancer (a maximum of 2 Lumicell DVS-guided (or LUM-guided) shaves per lumpectomy cavity orientation). In the control arm, the surgeon did not use the Lumicell DVS to guide additional resection of tissue. Randomization to study arms was performed at a ratio of 10:1; that is, on average for every 10 patients randomized to the Lumicell DVS arm, one patient was randomized to the control arm. The control group was included with the intent of reducing potential bias from surgeons that could arise if surgeons knew that the Lumicell DVS was going to be used in all patients. The control arm was not used to compare results with the treatment arm. Also, because the Lumicell DVS is used after the surgeon completes their SoC BCS in the treatment arm, the patients serve as their own control.

All clinical staff were informed whether the patient was randomized to the treatment or control arm after the surgeon completed the planned SoC BCS. Pathologists were blinded to whether the shave undergoing histopathology examination was an SoC shave or a LUM-guided shave.

The Pivotal study was statistically powered for the three coprimary effectiveness endpoints*:* removal of residual cancer, tissue-level sensitivity, and tissue-level specificity. For the primary endpoint of the proportion of patients with residual cancer removed in at least one LUM-guided shave, success was declared if the lower bound of the 95% confidence interval (CI) of this proportion was greater than 3%. For the primary endpoints of tissue-level sensitivity and specificity, success was declared if the lower bound of the 95% CI for tissue-level sensitivity was greater than the performance goal of 40%, and if the lower bound of the 95% CI for tissue-level specificity was greater than the performance goal of 60%. All of the three primary endpoints were tested at a one-sided significance level of 2.5%. For further information regarding the clinical endpoints see Section 3 below.

Patients were enrolled until approximately 70 truth standard positive events were reported to achieve the desired statistical power, up to a maximum of 450 patients. The number of truth standard positive events were counted based on the truth standard hierarchical approach.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Pivotal Study was limited to patients who met the following inclusion criteria:

- Female, 18 years or older with histologically or cytologically confirmed primary invasive breast cancer, ductal carcinoma in situ (DCIS), or primary invasive breast cancer with a DCIS component
- Patients were scheduled for a lumpectomy for a breast malignancy
- Patients were able and willing to follow study procedures and instructions
- Patients received and signed an informed consent form
- Patients had no uncontrolled serious medical problems except for the diagnosis of breast cancer
- Patients had organ and marrow function within limits as defined below:
  - Leukocytes > 3,000/mcL
  - Platelets > 75,000/mcL
  - Total bilirubin within normal institutional limits
  - AST (SGOT)/ALT (SGPT) < 2.5 X institutional upper limit of normal
  - Creatinine ≤ 1.5 mg/dL or creatinine clearance > 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
- Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Patients were not permitted to enroll in the Pivotal Study if they met any of the following exclusion criteria:

- Patients who had been diagnosed with bilateral breast cancer and were undergoing a bilateral resection procedure
- Patients who were pregnant at the time of diagnosis of their breast cancer; this exclusion is necessary because the teratogenic properties of LUMISIGHT are unknown. Because there is an unknown but potential risk of AEs in nursing infants secondary to treatment

of the mother with LUMISIGHT, breastfeeding should be discontinued if the mother is treated with LUMISIGHT

- Patients who were sexually active and not willing/able to use two medically acceptable forms of contraception (hormonal, barrier method of birth control, abstinence) upon entering the study and for 60 days after injection of LUMISIGHT. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Breast cancer patients are routinely advised against becoming pregnant during treatment, so this requirement does not differ from SoC
- Patients who had taken an investigational drug within 30 days of enrollment
- Patients who had administration of methylene blue or any dye for sentinel lymph node mapping on the day of the surgery prior to imaging the lumpectomy cavity with the Lumicell DVS
- Patients who had not recovered from AEs due to other pharmaceutical or diagnostic agents
- Patients with uncontrolled hypertension defined as persistent systolic blood pressure > 180 mm Hg, or diastolic blood pressure > 110 mm Hg; those patients with known hypertension should be stable with controlled hypertension while under pharmaceutical therapy
- History of allergic reaction to polyethylene glycol (PEG)
- History of allergic reaction to any oral or intravenous contrast agents
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, chronic obstructive pulmonary disease or asthma requiring hospitalization within the past 12 months, or psychiatric illness/social situations that would limit compliance with study requirements
- HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with LUMISIGHT
- Any patient for whom the investigator feels participation is not in the best interest of the patient
- Patients undergoing a second lumpectomy procedure because of positive margins in a previous surgery prior to entering the Pivotal Study
- Patients with post-biopsy hematomas greater or equal to 2 cm that are visible on physical exam or detected during pre-operative observations
- Patients with prior ipsilateral breast cancer surgeries, mastectomies, breast reconstructions, or implants
- Patients with prior ipsilateral reduction mammoplasties (breast reductions) performed less than 2 years prior to enrollment to this study

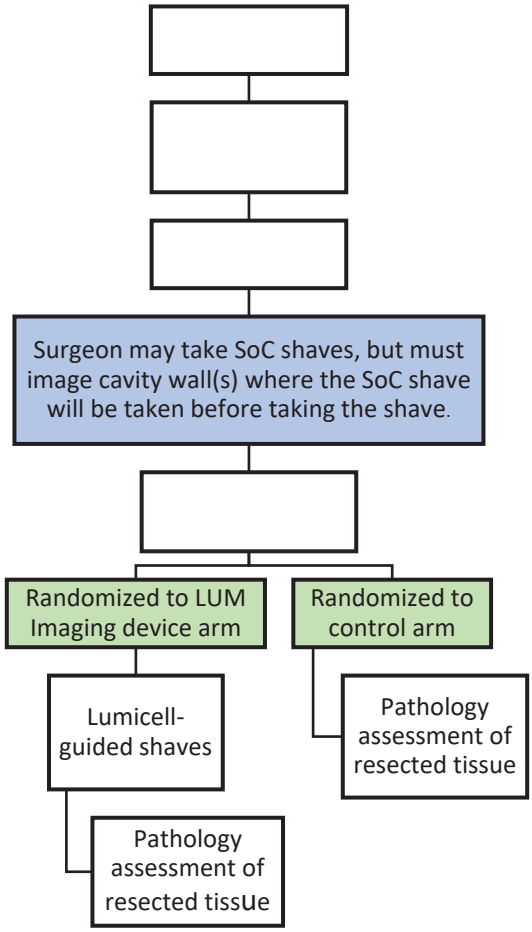
- Patients previously treated with systemic therapies to treat the cancer to be removed during this clinical investigation, such as neo-adjuvant chemotherapy or hormonal therapy
- Patients undergoing BCS whose resected specimen (main lump, shaves, or any other resected tissue) will be evaluated with frozen section after the Lumicell DVS-guided removal of shaves.

2. Study Procedure and Follow-up Schedule

The study procedure and surgical workflow is depicted in Figure 2 below.

Eligible patients consenting to participate in the study were injected with LUMISIGHT at a dose of 1.0 mg/kg 2-6 hours prior to the recording of any image.

Figure 2. Study Procedure Workflow



Once the SoC BCS procedure was completed, it was revealed whether the patient was randomized into the treatment arm or the control arm as below:

- **LUM Imaging Device Arm (or treatment arm)**: Patients who received 1 mg/kg LUMISIGHT, completed SoC BCS and had their lumpectomy cavity imaged with the Lumicell DVS for additional image-guided tissue (LUM-guided shaves)
- **Control Arm**: Patients who received 1 mg/kg LUMISIGHT, completed SoC BCS and had no Lumicell DVS imaging of the lumpectomy cavity.

After surgery was completed for patients in both the LUM Imaging Device Arm and the Control Arm, all resected specimens were sent to the pathology laboratory at each site for margin assessment per SoC.

All patients were observed for safety assessments of LUMISIGHT with standard preoperative, intraoperative, and postoperative monitoring after administration of the LUMISIGHT injection. Patients had a final safety assessment at their first postoperative visit. Final safety assessments for AEs and clinical laboratory evaluations were performed for all patients at the routine (first) postoperative visit as shown in the schedule of events (Table 5). All enrolled patients were followed in the study until their medical team determined that no further surgical intervention was required, and their postoperative follow-up and postoperative blood sample had been completed or until resolution of any reported AE related to the study intervention.

All study visits and assessments are summarized in Table 5.

Table 5. Schedule of Events for Study Visits and Assessments

	Pre-Enrollment / Screening	Day 1 / Enrollment	~2 - 14 Days After Surgery	Routine Follow-up Visit	3-Month PROM Survey Collection	6-Month PROM Survey Collection
Informed consent	X					
Medical history	X					
Radiologic evaluation[a]	X					
Physical exam (Ht, Wt, VS)	X					
Pregnancy test (serum or urine)	X[b]					
CBC with differentials	X			X		
Serum chemistry[c]	X			X		
Concomitant medications	X	X		X		

	Pre-Enrollment / Screening	Day 1 / Enrollment	~2 - 14 Days After Surgery	Routine Follow-up Visit	3-Month PROM Survey Collection	6-Month PROM Survey Collection
Adverse event/adverse device effect evaluation		X		X		
Patient Reported Outcome Measures Survey[d]		X[d]		X	X	X
LUMISIGHT administration		X				
Randomization		X				
Intraoperative imaging[e]		X				
Margin assessment			X			

Abbreviations: CBC = complete blood count; Ht = height; PROM = Patient Reported Outcome Measure; VS = vital signs; Wt = weight

[a] Radiologic evaluations are not required if not part of the patient's medical history

[b] Serum or urine pregnancy test (women of childbearing potential).

[c] Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen, calcium, chloride, glucose, potassium, total protein, aspartate transaminase (AST/SGOT), alanine transaminase (ALT/ SGPT), sodium and creatinine/creatinine clearance

[d] PROMs were optional for enrollment. The Baseline evaluation could be completed by the patient at any time prior to the lumpectomy procedure. A validated survey tool, the Breast-Q, was used to collect the majority of the PROMs.

[e] If patient is randomized into the Device Arm.

3. Clinical Endpoints

Safety Endpoints

To provide evidence of safety for LUMISIGHT and the Lumicell DVS, adverse events (AEs) and serious adverse events (SAEs) stratified by severity and relatedness to drug/device were evaluated.

Primary Effectiveness Endpoints

To provide evidence of effectiveness, three co-primary endpoints were used in the Pivotal Study:

- Removal of Residual Cancer: the proportion of patients who have residual cancer found in at least one LUM-guided shave

- Diagnostic performance measure of tissue-level sensitivity
- Diagnostic performance measure of tissue-level specificity

The Pivotal Study performance goal criteria for all three primary effectiveness endpoints were as follows:

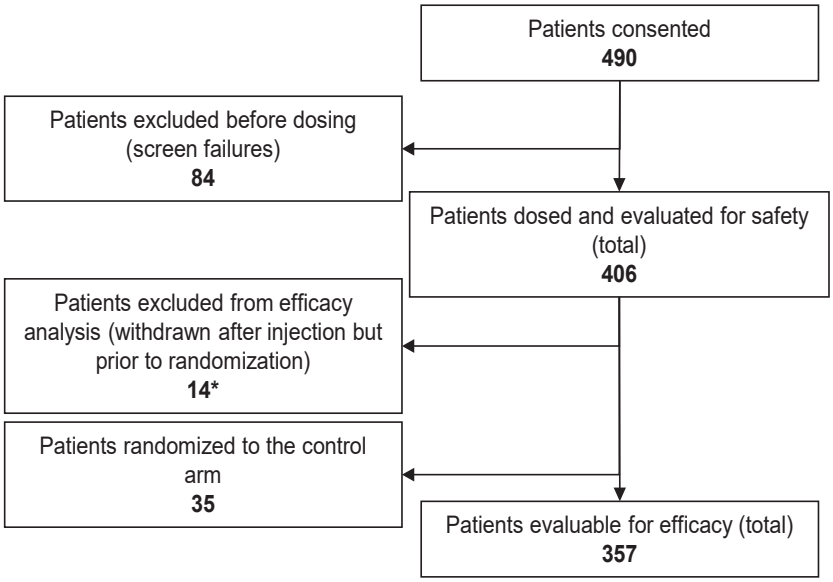
- Removal of Residual Cancer: the performance goal selection for this endpoint was pre-specified as greater than 3% for the lower bound of the 95% CI of this proportion
- Tissue-level sensitivity: the performance goal was pre-specified at greater than 40% for the lower bound of the 95% CI of the tissue-level sensitivity
- Tissue-level specificity: the performance goal was prespecified greater than 60% for the lower bound of the 95% CI of the tissue-level specificity

B. Accountability of PMA Cohort

At the time of database lock, 406 patients had enrolled in the PMA study and received a single intravenous dose of LUMISIGHT. A total of 392 patients were randomized to either the LUM Imaging Device Arm (n = 357) or Control Arm (n = 35). Fourteen (14) patients were withdrawn from the study after injection of LUMISIGHT but before randomization (Figure 3).

The evaluation of effectiveness was based on the 357 patients randomized to the LUM Imaging Device and the primary analysis set was the modified intent-to-treat (mITT) Population comprising all patients who completed the study procedure (n = 357). Evaluation of safety included all patients that were injected with LUMISIGHT (n = 406).

Figure 3. Pivotal Study Accountability Tree



*Withdrawals were due to adverse events (n = 7), device system issues (n = 2), physician decision (n = 1), protocol deviations (n = 4).

C. Study Population Demographics and Baseline Parameters

Patient demographic characteristics are presented in Table 6; and the tumor characteristics are presented in Table 7.

Overall, demographic characteristics data of the enrolled populations were representative of the US population of newly diagnosed patients with breast cancer. The distribution of age, sex, race, ethnicity, and the calculated body mass index (BMI) were found to be very similar between the study populations.

Table 6. Study Population Disposition and Demographics

Characteristics	LUMISIGHT Injected (Safety Analysis Population) (N = 406)	Modified Intent-to-Treat Population (N = 357)	Control Group (N = 35)
Sex			
Female	406 100.0%	357 100.0%	35 (100.0%
Age (years)			
Mean ± SD (N)	62.3 ± 9.7 (406)	62.4 ± 9.6 (357)	61.6 ± 9.9 (35)
Median (Q1, Q3)	64.0 (56.0, 70.0)	64.0 (57.0, 70.0)	62.0 (54.0, 70.0)
Range (Min, Max)	(36.0, 83.0)	(36.0, 83.0)	(37.0, 82.0)

Characteristics	LUMISIGHT Injected (Safety Analysis Population) (N = 406)	Modified Intent-to-Treat Population (N = 357)	Control Group (N = 35)
Race n (%)			
American Indian or Alaska Native	1 0.2%	0	1 (2.9%
Asian	22 (5.4%	21 (5.9%	1 (2.9%
Black or African American	26 (6.4%	22 (6.2%	4 (11.4%
Native Hawaiian or Pacific Islander	1 0.2%	1 0.3%	0
White	337 83.0%	297 83.2%	27 (77.1%)
Other	4 1.0%	4 1.1%	0
Unknown or not reported	15 (3.7%	12 (3.4%	2 (5.7%
Ethnicity n (%)			
Hispanic or Latino	12 (3.0%	11 (3.1%	1 (2.9%
Non-Hispanic or Latino	383 94.3%	336 94.1%	34 97.1%)
Unknown or not reported	11 (2.7%	10 (2.8%	0
Body Mass Index (kg/m^2)			
Mean ± SD (N)	29.9 ± 6.6 (405)	29.8 ± 6.7 (356)	31.0 ± 5.9 (35)
Median (Q1, Q3)	29.4 (25.0, 33.8)	29.2 (25.0, 33.3)	30.8 (26.1, 36.0)
Range (Min, Max)	(16.8, 67.4)	(16.8, 67.4)	(20.0, 42.5)

Abbreviations: Max = maximum; Min = minimum; Q = quartile; SD = standard deviation

Table 7. Baseline Clinicopathological Findings: Tumor Histology and Receptor Status from Biopsy or Main Specimen

Characteristics	Safety Analysis Population (N = 406)	Modified Intent-to-Treat Population (N = 357)	Control Population (N = 35)
Largest Dimension of Tumor in Main Specimen (cm)			
Mean ± SD (N)	1.8 ± 1.4 (378)	1.7 ± 1.3 (344)	2.2 ± 1.5 (34)
Median (Q1, Q3)	1.5 (0.9,2.2)	1.5 (0.9,2.1)	1.9 (1.0,3.1)
Range (Min, Max)	(0.1,10.1)	(0.1,10.1)	(0.4,8.3)
Tumor Histology (Biopsy and/or Main Lumpectomy Specimen)			

Characteristics	Safety Analysis Population (N = 406)	Modified Intent-to-Treat Population (N = 357)	Control Population (N = 35)
DCIS Only	78 (19.2%)	70 (19.6%)	6 (17.1%
IDC ± DCIS	284 70.0%	249 69.7%	25 71.4%)
ILC ± DCIS	41 (10.1%)	35 (9.8%	4 (11.4%
IDC + ILC	3 (0.7%	3 0.8%	0
Receptor Status			
ER (+)	378 93.1%	335 93.8%	30 (85.7%)
PR (+)	311 76.6%	272 76.2%	28 (80.0%)
HER2 (+)	23 (5.7%	20 (5.6%	3 8.6%
Triple Negative			
Yes	15 (3.7%)	11 (3.1%	3 8.6%
No	391 96.3%	346 96.9%	32 (91.4%)
Unknown	0	0	0
Lymph Nodes			
Lymph Node (+)	10 (2.5%	9 2.5%	1 2.9%
Lymph Node (-)	60 (14.8%)	51 (14.3%)	7 (20.0%
No Lymph Node Biopsy	336 82.8%	297 83.2%	27 (77.1%)

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptors; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; Max = maximum; Min = minimum; PR = progesterone receptor: Q = quartile

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 406 patients that received an intravenous dose of 1 mg/kg LUMISIGHT. The key safety outcomes for the study are presented below. Adverse event (AE) data are reported in Table 8.

Adverse Events

A total of 596 AEs were reported in 406 patients in the safety population with 395 AEs reported as related to LUMISIGHT. There were no device related adverse events reported.

Of the 395 AEs related to LUMISIGHT, the most common AE was chromaturia (abnormal color of urine) at an incidence rate of 90.4% (367 of 406 patients). Chromaturia was an expected AE

due to the blue color of the LUMISIGHT injection solution and resolved between 24 and 48 hours after administration in over 92% of the patients; the longest time for resolution was six days.

Other than chromaturia, 23 patients experienced 28 AEs related to LUMISIGHT, with no event that was determined to be related to the intervention having an incidence rate of more than 1.0%. All AEs for all patients resolved during the study.

No deaths and no unexpected severe events related to LUMISIGHT were reported. No serious or nonserious unanticipated adverse device effects (UADE) were observed in the study.

The second most common adverse reaction was hypersensitivity, occurring in six patients (approximately 1.5%; Table 8). This included one patient who experienced anaphylaxis.

Table 8. Summary of Adverse Reactions by Preferred Term

Adverse Event Preferred Term[a]	**Patients (%) (N = 406)**
Chromaturia	367 90.4%
Hypersensitivity	6 (1.5%)
Nausea	2 (0.5%
Dysgeusia	1 (0.2%
Dyspnea	1 (0.2%
Pyrexia	1 (0.2%
Skin discoloration after extravasation	1 (0.2%
Vomiting	1 (0.2%

Note: Patients with multiple events in the same category are counted only once in that category.
[a]MedDRA Version 22.1

2. Effectiveness Results

The analysis of effectiveness was based on the 357 evaluable patients in the mITT Population who completed the study. Key effectiveness outcomes are presented in Table 9 to Table 12.

Primary Endpoint Analysis

Removal of Residual Cancer

LUMISIGHT and the Lumicell DVS demonstrated success in detecting residual cancer and guiding the removal of the cancerous tissue that would have otherwise remained undetected after SoC BCS in 27 patients (7.6%) in the mITT Population.

- A total of 27 of 357 patients had residual cancer found in at least one LUM-guided shave in the mITT Population (7.6%; 95% CI: 5.0%, 10.8%). The performance goal for the primary endpoint, Removal of Residual Cancer, was met for the LUMISIGHT and

Lumicell DVS with a lower bound CI of 5.0%, which was greater than the pre-set performance goal of 3% (Table 9).

Tissue-level Sensitivity and Tissue-level Specificity

The diagnostic performance endpoints of the Lumicell DVS were as follows:

- Tissue-level sensitivity was 49.1% (34 out of 69 truth standard positives; 95% CI: 36.4%, 61.9%)
- Tissue-level specificity was 86.5% (1,940 out of 2,277 truth standard negatives; 95% CI: 84.5%, 88.3%).

The tissue-level sensitivity endpoint did not meet the pre-set performance goal of 40% by 3.6 percentage points at the lower bound of the 95% CI (i.e., 36.4%). The tissue-level specificity endpoint successfully met the pre-set performance goal of 60% by 24.5 percentage points at the lower bound of the 95% CI (i.e., 84.5%). Sensitivity and specificity results were calculated using the generalized estimating equation [GEE] method to account for within-patient correlations (Table 9).

Table 9. Primary Effectiveness Endpoint Results (Pivotal Study)

Primary Effectiveness Endpoints	Performance Goal (Lower Bound of 95% Confidence Interval)	Results
Removal of Residual Cancer: Proportion of patients who have residual cancer found in at least one LUM-guided shave among all patients in the LUM Imaging Device Arm (patient-level)	> 3%	27/357 7.6% 95% CI: 5.0%, 10.8%
Tissue-level Sensitivity (GEE method[a])	> 40%	34/69 49.1% 95% CI: 36.4%, 61.9%
Tissue-level Specificity (GEE method[a])	> 60%	1,940/2,277 86.5% 95% CI: 84.5%, 88.3%

Abbreviations: CI = confidence interval; GEE = generalized estimating equations; LUM-guided shaves = Lumicell DVS guided shaves

[a]GEE method was used to calculate sensitivity and specificity to account for within-patient correlations.

Other Endpoint Analysis: Secondary Effectiveness Endpoints

A series of secondary effectiveness endpoints were analyzed in the Pivotal Study/PMA clinical study related to meaningful clinical impact. The results of these analyses are presented in Table 10 to Table 12.

Table 10. Detection and Conversion of Positive Standard of Care Margin by the Lumicell DVS

	mITT Population (LUM Imaging Device Arm)
Total Patients	357
Patients having positive margins after SOC BCS n %	62 (17.4%) 95% CI:13.6%, 21.7%
Detection of all positive margins after SoC BCS on the corresponding orientations in the cavity	
Secondary endpoint *a*: Proportion of patients with positive margins after SoC BCS for whom all the orientations with positive SoC margins were detected in the cavity by the Lumicell DVS n (%	16.1% (10/62) 95% CI: 8.0%, 27.7%
Conversion of all positive margins after SoC BCS to negative margins by removing LUM-guided shaves	
Secondary endpoint *b*: Proportion of patients with pathology-positive margins after SoC BCS for whom additional Lumicell DVS-guided shaves resulted in pathology-negative margins n (%	14.5% (9/62) 95% CI: 6.9%, 25.8%
Additional analyses	
Detection of at least one positive margins after SoC BCS on the corresponding orientations in the cavity	
Proportion of patients with positive margins after SoC BCS for whom at least one orientation with positive an SoC margin was detected in the cavity by the Lumicell DVS n %	24.2% (15/62) 95% CI: 14.2%, 36.7%

Abbreviations: BCS = breast-conserving surgery; CI = confidence interval; mITT = modified Intent-to-Treat; SoC = standard of care

Table 11. Removal of Residual Cancer Guided by the Lumicell DVS in Patients with Negative and Positive Margins after Standard of Care Surgery

	mITT Population
All Patients	357
Patients Having All Negative Margins after SoC BCS	295
Patients Having at Least One Positive Margin after SoC BCS	62
Patients with negative margins after SoC BCS having tumor found in at least one therapeutic shave	
Secondary endpoint *d*: Ratio of patients with negative margins after the SoC procedure who have residual cancer found in at least one LUM-guided shave among patients with negative margins n (%	6.4% (19/295 95% CI: 3.9%, 9.9%
Additional analyses in patients with positive margins after SoC BCS	
Patients with positive margin after SoC BCS having tumor found in at least one therapeutic shave	
Ratio of patients with positive margins after the SoC procedure who have residual cancer found in at least one LUM-guided shave n %)	12.9% (8/62) 95% CI: 5.7%, 23.9%
Ratio of patients with positive margins after the SoC procedure who have residual cancer found in at least one LUM-guided shave among all patients n (%)	2.2% 8/357 95% CI: 1.0%, 4.4%

Abbreviations: BCS = breast-conserving surgery; CI = confidence interval; mITT = modified Intent-to-Treat; SoC = standard of care

Table 12. Summary of Tissue Volumes: Lumpectomy, Standard of Care Shaves, LUM-guided Shaves and Contribution to Total Tissue Volume

	Treatment Arm		
	mITT Population	**mITT Population and having at least one LUM-guided shave removed**	**Control**
All Patients N	357	166	35
Lumpectomy Volume (cm^3)			
Mean (SD)	74.9 (76.5)	70.5 (55.9)	82.0 (65.0)
Median (2.5%, 97.5%)	54.0 (9.7, 267.2)	54.3 (13.3, 208.0)	66.8 (10.5, 308.0)
Median (Min, Max)	54.0 (5.5, 722.6)	54.3 (6.0, 463.0)	66.8 (10.5, 308.0)
SoC Shave Volume (cm^3)			
Mean (SD)	14.1 (36.7)	16.3 (24.0)	13.5 (16.8)
Median (2.5%, 97.5%)	7.5 (0.0, 71.2)	9.8 (0.0, 77.0)	7.7 (0.0, 71.9)
Median (Min, Max)	7.5 (0.0, 603.0)	9.8 (0.0, 164.6)	7.7 (0.0, 71.9)
SoC Total Volume (cm^3)			
Mean (SD)	89.0 (93.7)	86.8 (70.0)	95.6 (68.8)
Median (2.5%, 97.5%)	66.4 (15.1, 308.7)	70.6 (20.6, 253.3)	76.7 (21.9, 308.0)
Median (Min, Max)	66.4 (5.5, 963.0)	70.6 (6.0, 601.4)	76.7 (21.9, 308.0)
Secondary Endpoint *f*: Therapeutic Shave Volume (cm^3)			
Mean (SD)	10.1 (17.5)	21.8 (20.1)	0.0 (0.0)
Median (2.5%, 97.5%)	0.0 (0.0, 61.1)	15.6 (1.6, 73.5)	0.0 (0.0, 0.0)
Median (Min, Max)	0.0 (0.0, 126.7)	15.6 (0.7, 126.7)	0.0 (0.0, 0.0)
Total Volume (cm^3)			
Mean (SD)	99.1 (97.3)	108.6 (79.0)	95.6 (68.8)
Median (2.5%, 97.5%)	77.5 (15.2, 348.1)	90.0 (28.3, 318.1)	76.7 (21.9, 308.0)
Median (Min, Max)	77.5 (5.5, 963.0)	90.0 (13.7, 625.8)	76.7 (21.9, 308.0)
Secondary Endpoint *g*: Ratio of Therapeutic Shave Contributing to Total Volume			
Mean (SD)	9.4% 14.1%	20.3% (14.5%)	0% 0%
Median (2.5%, 97.5%)	0.0% (0.0%, 44.7%)	16.7% (3.3%, 61.9%)	0.0% 0.0%, 0.0%)
Median (Min, Max)	0.0% (0.0%, 81.3%)	16.7% (1.7%, 81.3%)	0.0% 0.0%, 0.0%)

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; mITT = modified Intent-to-Treat; SD = standard deviation, SoC = standard of care

For exploratory analysis, the patient reported outcome measures (PROM) data collected using the validated BREAST-Q survey, module 2, version showed that the majority of the patients responded either “very satisfied” or “somewhat satisfied” across all the time frames pre- and post-surgery. In addition, PROMs were generally similar between those patients with or without LUM-guided therapeutic shaves. No statistically significant difference between the patient overall satisfaction across the two groups was observed.

Other Endpoint Analysis: Post hoc Effectiveness Endpoints

Total Number of Patients with Residual Cancer Removed in Second Surgeries and Guided by the Lumicell DVS

Overall, after the SoC BCS was complete, 41 subjects had residual cancer removed either by a re-excision surgery or a LUM-guided shave (Table 13). Of these, 14 subjects had residual cancer removed only during the re-excision surgery and seven subjects had residual cancer removed by both LUM-guided shaves and re-excision surgeries. An additional 20 subjects had residual cancer removed only by LUM-guided shaves. Thus, 27 out of 41 subjects (65.9%) had additional cancer resection enabled by the Lumicell DVS, further demonstrating that the combination product can enhance SoC surgery.

Table 13. Number of Subjects with Residual Cancer Removed

Total subjects with residual cancer removed after SoC BCS (n)	41
Subjects with residual cancer removed only in a re-excision surgery n (%	14 (34.1%)
Subjects with residual cancer removed by LUM-guided shaves and re-excisions n %)	7 (17.1%)
Subjects with residual cancer removed only by LUM-guided shaves n %)	20 48.8%)

Abbreviations: BCS = breast-conserving surgery; SoC = standard of care

Characteristics of Tumor Detected in LUM-guided Shaves from Standard of Care Negative Margin Orientations

The characteristics of the residual cancer removed by LUM-guided shaves were evaluated, specifically from subjects with orientations that had a negative margin assessment after the SoC procedure. This analysis focused on this subset population because the cancer detected by the Lumicell DVS most likely would have not been removed by any other surgical procedure. This group consisted of 22 subjects including:

- 19 subjects with all SoC negative margins with residual cancer removed guided by the Lumicell DVS

- Three subjects with SoC positive margins but residual cancer removed guided by the Lumicell DVS from orientations with an SoC negative margin that potentially would not be addressed in a second surgery

These 22 subjects had residual cancer removed that would have not been otherwise detected with the current SoC procedures. The characteristics of the subjects and details of tumor burden, tumor grade, and margin status are presented in Table 14. Of these, 21 subjects (95.0%, 21 out of 22 subjects) had potential clinically significant factors including:

- Residual cancer removed was non-microscopic in size (1 mm to 13 mm)
- Tumor was Grade 3, or
- The subject was 70 years of age or older and ER-positive, for which adjuvant radiation may have been omitted according to the American Society for Radiation Oncology (ASTRO) evidence-based guidelines (Smith BD et al. 2018).

In these subjects, the Lumicell DVS detected and guided the removal of residual cancer that otherwise remained undetected by the SoC procedure.

Table 14. Summary of Subjects with Residual Cancer Removed in LUM-guided Shaves by Tumor Burden, Tumor Grade, Age, and Standard of Care Margin Status

Subject	Largest Tumor Dimension Found in LUM-guided Shave [a]	Tumor Grade [a]	Age [b]	SoC Margin Status [a]
01-01-PIV-0012	Not reported[c]	**3**	58	Negative
01-01-PIV-0023	Not reported[c]	**3**	42	Negative
01-01-PIV-0034	**1.5 mm**	**3**	51	Negative
01-01-PIV-0038	**2 mm**	2	65	Negative
01-01-PIV-0044	**2 mm**	**3**	58	Negative
01-01-PIV-0055	**11 mm**	2	**76**[d]	Negative
04-01-PIV-0050	**2 mm**	**3**	36	Negative
06-01-PIV-0004	**6.5 mm**	2	**71**[d]	Negative
13-01-PIV-0019	**4 mm**	2	52	Negative
14-01-PIV-0011	**1 mm**	**3**	**71**[d]	Negative
14-01-PIV-0022	**1.5 mm**	1	53	Negative
14-01-PIV-0031	**1 mm**	2	60	Negative
14-01-PIV-0048	**11 mm**	**3**	58	Negative
14-01-PIV-0061	Not reported[c]	1	**77**[d]	Negative
18-01-PIV-0013	**1 mm**	**3**	47	Negative
22-01-PIV-0003	**2 mm**	**3**	**70**[d]	Negative

Subject	Largest Tumor Dimension Found in LUM-guided Shave [a]	Tumor Grade [a]	Age [b]	SoC Margin Status [a]
23-01-PIV-0015	**13 mm**	2	52	Negative
14-01-PIV-0084	**7 mm**	Not reported[c]	66	Negative
14-01-PIV-0056	**7 mm**	2	60	Positive[e]
18-01-PIV-0027	**5 mm**	2	65	Positive[e]
18-01-PIV-0081	**8 mm**	2	66	Positive[e]
13-01-PIV-0004	Not reported[c]	2	59	Negative

Abbreviations: CI = confidence interval; SoC = standard of care
[a]Data from pathology chart
[b]Demographic data from Electronic Data Capture
[c] Not reported indicates data not entered in the subject's study Case Report Form.
[d] These subjects are at least 70 years old and estrogen-receptor positive
[e] These subjects had positive margins but a LUM-guided shave with tumor was removed from a negative margin orientation

3. Pivotal Study Safety and Effectiveness Conclusions

Overall, the evaluation of safety in the Pivotal Study showed that the study treatment LUMISIGHT was associated with an incidence of hypersensitivity of approximately 1.5% (6/406), including one patient with anaphylaxis. Refer to the LUMISIGHT prescribing information for additional information, warnings, and recommendations.

- Chromaturia was the most commonly reported and expected AE due to the blue color of the LUMISIGHT injection that resolved completely in approximately 92% of patients within 48 hours.

LUMISIGHT and Lumicell DVS demonstrated success in detecting and guiding the removal of residual cancer that would have otherwise remained after SoC BCS in 27 out of 357 7.6%) patients in the mITT Population (95% CI: 5%, 10.8%).

- The performance goal for the primary endpoint Removal of Residual Cancer was met for the Lumicell DVS with a lower bound CI of 5%, which was greater than the pre-set performance goal of 3%.

The primary endpoints that measured diagnostic performance confirmed:

- Tissue-level sensitivity of 49.1% (34 out of 69 truth standard positives; 95% CI: 36.4%, 61.9%; GEE Estimator)
- Tissue-level specificity of 86.5% (1940 out of 2277 truth standard negatives; 95% CI: 84.5%, 88.3%; GEE Estimator).

The tissue-level sensitivity endpoint did not meet the pre-set performance goal of 40% by 3.6 percentage points at the lower bound of the 95% CI (i.e., 36.4%). The tissue-level specificity endpoint successfully met the pre-set performance goal of 60% by 24.5 percentage points at the lower bound of the 95% CI (i.e., 84.5%).

LUMISIGHT and Lumicell DVS also demonstrated the ability to detect LUM-positive signals corresponding to SoC negative margin orientations.

- In 19 out of 295 (6.4%) patients with negative margins at the end of the SoC procedure, the LUMISIGHT and Lumicell DVS detected and guided the removal of shaves containing residual cancer. This represented 5.3% of the entire mITT Population (19 of 357 patients). Without the use of the Lumicell DVS imaging device, these 19 patients would have completed their initial surgical procedure with cancer remaining in the lumpectomy cavity and would likely have not had an indication for a second surgery to address this remaining cancer.

The combination product also detected LUM-positive signals corresponding to SoC positive margin orientations and converted those orientations into negative margins by removing LUM-guided shaves (mITT Population) with subsequent reductions in positive margins after second surgeries.

- Subset analysis in patients with positive margins after SoC BCS further demonstrated that in 8 of 62 patients (12.9%) who had SoC positive margins identified by pathology, residual cancer was detected by the Lumicell DVS and removed by the surgeon. A total of 9 out of 62 (14.5%) patients with SoC positive margins were converted to having pathology-negative margins after LUM-guided resections. Although residual cancer may be removed in a second surgery due to positive margins in this subset of patients, eliminating it during the initial surgery can avoid the risk of not finding the exact location of residual cancer in a second surgery, in addition to potentially preventing a second surgery and the associated comorbidities with a second surgery.

Overall, 27 patients (out of 357) had residual cancer removed in LUM-guided shaves with 20 of those 27 patients having residual cancer only found by the Lumicell DVS..

A total of 41 patients had residual cancer removed after the SoC BCS was completed, with 65.9% of these patients having additional tumor resection enabled by using the LUMISIGHT and Lumicell DVS as adjunct to SoC BCS, further demonstrating that the device can enhance SoC surgery.

Among the 166 patients with at least one LUM-guided shave excised, the mean total LUM-guided shave volume was 22 cm^3 ± 20 cm^3, accounting for 20% ± 15% of the total volume of resection. An exploratory Patient Reported Outcome Measure (PROM) based on a module of the BREAST-Q survey indicated there was no significant difference in patient overall satisfaction between patients with or without LUM-guided shaves for each PROM time frame.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 62 investigators listed on FDA Form 1572. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental clinical information includes:

1. Supportive Phase C IDE Feasibility Study CL0006
2. Pooled analyses of safety in clinical studies evaluated
3. Early clinical development: Phase 1 IND, IDE Feasibility Studies Phase A and B

1. Supportive Phase C IDE Feasibility Study CL0006

A Phase C Feasibility Study CL0006 was conducted to evaluate the safety and effectiveness of the LUMISIGHT and Lumicell DVS combination product and to train surgeons and clinical staff in preparation for the Pivotal Study. The safety and effectiveness data from this supportive clinical study are provided below. This study was not adequate and well-controlled. The performance data provided a basis for design of the pivotal trial. The performance results were generally aligned with those from the pivotal trial.

A. Study Title

Feasibility Study Phase C: Expansion into multiple institutions for training in the use of the Lumicell DVS for intraoperative detection of residual cancer in the tumor bed of female patients with breast cancer.

B. Overview of Phase C Feasibility Study CL0006

In this multicenter, open label, single arm study, patients were enrolled between 06 February 2018 and 15 August 2019. Database lock was on 10 April 2020.

This study was conducted at 16 sites within the United States of America with up to 250 patients planned to be enrolled.

C. Patient Disposition

A total of 234 patients received a single dose of LUMISIGHT (pegulicianine) in the safety analysis population; four patients were withdrawn prior to imaging with the Lumicell DVS.

A total of 230 patients completed the study in the mITT Population (Table 15).

Table 15. Patient Disposition in Phase C IDE Study CL0006

Disposition	Number of Patients
Patients with informed consent form signed	**283**
Patients exit prior to LUMISIGHT injection n %)	49 (17.3%)
Screen failure n %)	42 (14.8%)
Withdrawn prior to enrollment n %	7 (2.5%)
Patients with LUMISIGHT injected (SAF population) n (%)	**234 (82.7%)**
Patients withdrawn prior to LUM imaging procedure completed n (%)	4 (1.4%)
Patients completed with LUM imaging (mITT population) n (%)	**230 (81.3%)**
Patients with major protocol deviations n (%)	5 (1.8%)
Patients in the per protocol population n (%)	**225 (79.5%)**

mITT = modified intent-to-treat; SAF = safety analysis

D. Study Objectives

The key objectives of the study were to complete hands-on training of the surgeons and clinical staff who would be participating in the Pivotal Study, to evaluate the safety and effectiveness of LUMISIGHT and Lumicell DVS in breast cancer surgeries, and to identify and address any site-specific or user-specific issues for using the combination product in breast cancer surgeries.

E. Clinical Endpoints

Safety: All patients were observed to assess the safety of LUMISIGHT with standard preoperative, intraoperative, and postoperative monitoring from the time of injection of LUMISIGHT to the time they were discharged from the hospital. Patients had a final safety assessment at the first postoperative visit, at which time blood and urine laboratory studies were collected. Any reported AEs were followed until resolution.

Effectiveness: As the study was intended as a feasibility study to train surgeons and refine the patient calibrated tumor detection software, no predefined hypothesis-tested effectiveness criteria were used. However, effectiveness metrics were evaluated post hoc based on the Pivotal Study design and are presented in tables comparing the results between the two studies. The endpoints included in this comparative analysis included:

- Rate of removal of residual cancer at a per-patient level
- Diagnostic performance characterized as sensitivity and specificity at a per-image level
- Rate of detection of positive margins at a per-patient level
- Rate of conversion of positive margins to negative margins at a per-patient level
- Rate of removal of residual cancer in patients having negative SoC margins
- Average volume of LUM-guided shaves and contribution to total excision volume.

F. Study Design and Methodology

Design: Open label, single arm (non-randomized), multicenter clinical study.

Methodology: Planned number of patients: 250; total number of patients enrolled: 234.

The assessment for completing the surgical training was done in collaboration between Lumicell and each surgeon. A total of 1-3 surgeons per site were included in the training from 16 sites, with each surgeon allocated five patients per surgeon. Surgeons could enroll more than five patients if needed to complete training, or if more patients were needed to complete the patient calibrated tumor detection software verification.

Patients undergoing a lumpectomy procedure to treat primary breast cancer were injected with LUMISIGHT 2-6 hours prior to surgery at a dose of 1.0 mg/kg. The sequence of events during the surgical procedure varied based on the SoC used by the surgeon.

During surgery, patients received the SoC procedures for each site, including any SoC shaves. Then, the Lumicell DVS was used and Lumicell DVS-positive tissue was removed.

Data were collected to determine the margin assessment after the SoC lumpectomy procedure was completed (SoC margin), after the LUM imaging procedure was completed (final margin), and before the Lumicell DVS was used to guide the resection of additional tissue. All the resected tissue was to be handled and processed for margin assessment following the institution's practices for breast-conserving surgeries.

Inclusion and Exclusion Criteria

Enrollment in the Phase C IDE Feasibility Study CL0006 was limited to patients who met the following inclusion criteria:

- Patients must have had histologically or cytologically confirmed primary invasive breast cancer, DCIS, or a combination of invasive breast cancer and DCIS. The protocol accepted methods for obtaining the histological samples were diagnostic core needle biopsies or fine needle biopsies.
- Female, age of 18 years or older. Because no dosing or AE data are currently available on the use of LUMISIGHT in patients <18 years of age, children were excluded from this study.
- Patients must have been scheduled for a lumpectomy for a breast malignancy.

- Patients must have been able and willing to follow study procedures and instructions.
- Patients must have received and signed an ICF.
- Patients must have had no uncontrolled serious medical problems except for the diagnosis of cancer, as per the exclusion criteria listed below.
- Patients must have had normal organ and marrow function within limits as defined below:
    - Leukocytes > 3,000/mcL
    - Platelets > 75,000/mcL
    - Total bilirubin within normal institutional limits
    - AST (SGOT)/ALT (SGPT) < 2.5 X institutional upper limit of normal
    - Creatinine ≤ 1.5 mg/dL or creatinine clearance > 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were not permitted to enroll in the Phase C IDE Feasibility Study CL0006 if they met any of the following exclusion criteria:

- Patients who were treated for bilateral breast cancer resection procedure.
- Patients who were pregnant at the time of diagnosis of their breast cancer; this exclusion was necessary because the teratogenic properties of LUMISIGHT are unknown. Because there was an unknown but potential risk of AEs in nursing infants secondary to treatment of the mother with LUMISIGHT, breastfeeding should have been discontinued if the mother was treated with LUMISIGHT.
- Patients who were sexually active and not willing/able to use medically acceptable forms of contraception (hormonal or barrier method of birth control, abstinence) upon entering the study and for 60 days after injection of LUMISIGHT. Should a woman have become pregnant or suspected she was pregnant while participating in this study, she should have informed her treating physician immediately. Breast cancer patients are routinely advised against becoming pregnant during treatment, so this requirement does not differ from SoC.
- Patients who had taken an investigational drug within 30 days of enrollment.
- Patients with prolonged corrected QT interval defined as greater than 480 ms.
- Patients who had administration of methylene blue or any dye for sentinel lymph node mapping on the day of the surgery prior to imaging the lumpectomy cavity with the LUM Imaging Device.
- Patients who had not recovered from AEs due to other pharmaceutical or diagnostic agents.

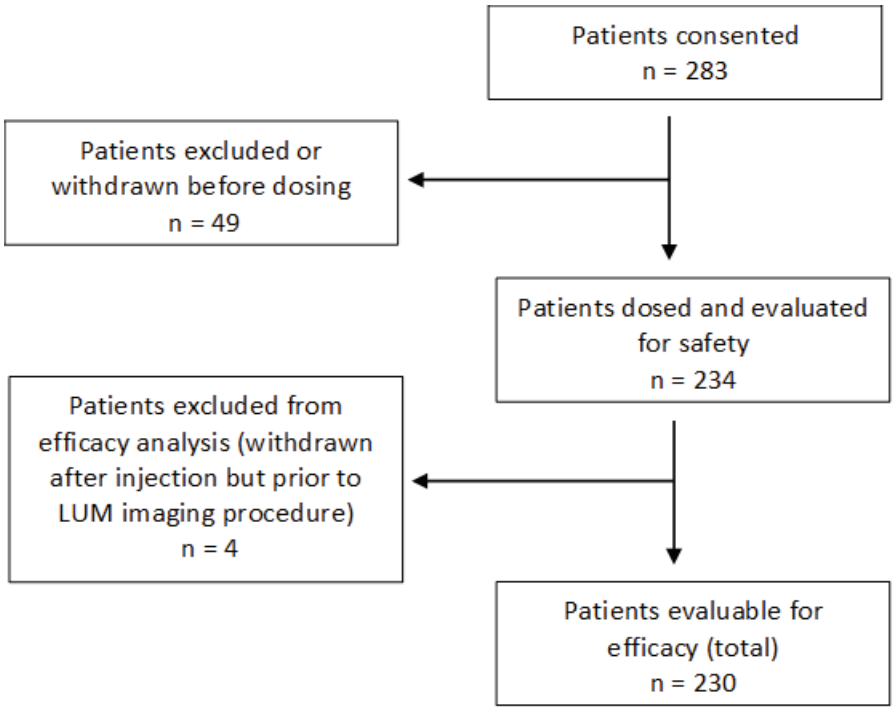
- Patients with uncontrolled hypertension defined as persistent systolic blood pressure > 180 mm Hg, or diastolic blood pressure > 110 mm Hg; those patients with known hypertension should have been stable within these ranges while under pharmaceutical therapy.
- History of allergic reaction to polyethylene glycol (PEG) (this criterion was added after the first case of anaphylaxis reported).
- History of allergic reaction to any oral or intravenous (IV) contrast agents (this criterion was added after the first case of anaphylaxis reported).
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, chronic obstructive pulmonary disease or asthma requiring hospitalization within the past 12 months, or psychiatric illness/social situations that would limit compliance with study requirements.
- Human immunodeficiency virus positive individuals on combination antiretroviral therapy were ineligible because of the potential for pharmacokinetic interactions with LUMISIGHT.
- Any patient for whom the investigator feels participation was not in the best interest of the patient.
- Patients undergoing a second lumpectomy procedure because of positive margins in a previous surgery prior to entering this study.
- Patients with prior ipsilateral breast cancer surgeries, mastectomies, breast reconstructions, or implants.
- Patients who had undergone a surgical biopsy for any reason in the ipsilateral breast performed less than 2 years prior to enrollment of this study.
- Patients with prior ipsilateral reduction mammoplasties (breast reductions) performed less than 2 years prior to enrollment to this study.
- Patients previously treated with systemic therapies to treat the cancer to be removed during this clinical investigation, such as neo-adjuvant chemotherapy or hormonal therapy.
- Patients undergoing breast conserving surgery whose resected specimen will be evaluated with frozen section.

G. Patient Accountability

At the time of database lock, of 234 patients enrolled in the Phase C IDE Feasibility Study CL0006 and who received a single intravenous dose of LUMISIGHT, 230 (98.3%) were available for analysis at the completion of the study (Table 16).

Four (4) patients were withdrawn from the study after injection of LUMISIGHT.

Figure 4. Phase C IDE Feasibility Study CL0006 Accountability Tree



To start the feasibility Phase C study, the patient-calibrated tumor detection software developed during the Phase B study was used. After the first 83 subjects were enrolled, the collected pathology results and Lumicell DVS imaging data were used to refine the patient calibrated tumor detection software, while enrollment continued. After a total of 127 subjects had been enrolled in the study, the refined tumor detection software was locked and implemented. The locked software was then used in the final 103 subjects in the feasibility Phase C study and in all the subjects in the pivotal study. As a result, the analysis populations for feasibility Phase C are defined as follows:

- Training Set (n = 83 subjects): consists of the initial 83 subjects enrolled in the feasibility Phase C study whose pathology and imaging data were used to refine the patient calibrated tumor detection software; these subjects used the patient calibrated tumor detection software developed during Phase B
- Extended Training Set (n = 127 subjects): consists of the initial 83 subjects in the Training Set plus 44 subjects enrolled before implementing the refined patient calibrated tumor detection software; all of these 127 subjects used the patient calibrated tumor detection software developed during Phase B
- Validation Set (n = 103): consists of 103 subjects enrolled after the refined and locked patient calibrated tumor detection software was implemented

- All population (n = 230): consists of subjects in the Extended Training Set and Validation Set; when efficacy results are presented for this population, the refined algorithm was implemented retrospectively to the Extended Training Set

H. Study Population Demographics and Baseline Parameters

The patient disposition and demographics of the study population are presented in Table 16 and the baseline clinicopathological findings are presented in Table 17.

Overall, the distribution of age, sex, race, ethnicity, and the calculated BMI were found to be very similar between the study populations.

Table 16. Phase C IDE Feasibility Study CL0006: Population Disposition and Demographics

Characteristics	Total LUMISIGHT Injected (SAF Population) (N = 234)	Total LUM Imaging Procedure Completed (mITT Population) (N = 230)
Patient Status		
Screen Failure	0	0
Complete	230 98.3%	230 100.0%
Withdrawn	4 (1.7%	0
Sex		
Female	234 100.0%	230 100.0%
Age (Years)		
Mean ± SD (N)	61.7±9.8 (234)	61.4±9.7 (230)
Median (Q1, Q3)	62.0 (55.0,69.0)	62.0 (55.0,69.0)
Range (min, max)	(37.0,84.0)	(37.0,84.0)
Race		
American Indian or Alaska Native	0	0
Asian	15 (6.4%	15 (6.5%
Black or African American	21 (9.0%	21 (9.1%
White or Caucasian	187 79.9%	183 79.6%
Multiple races	2 (0.9%	2 (0.9%
Unknown or Not reported	9 (3.8%	9 3.9%
Ethnicity		
Hispanic or Latino	4 (1.7%	4 (1.7%
Non-Hispanic or Latino	220 94.0%	216 (93.9)
Unknown or not reported	10 (4.3%	10 (4.3%
BMI (kg/m^2)		
Mean ± SD (N)	29.0±6.6 (233)	29.0±6.6 (229)
Median (Q1, Q3)	27.5 (24.3,32.3)	27.4 (24.3,32.2)
Range (min, max)	(17.1,51.3)	(17.1,51.3)

Table 17. Phase C IDE Feasibility Study CL0006: Baseline Clinicopathological Findings - Tumor Histology and Receptor Status from Biopsy or Main Specimen

Characteristics	Total LUM Imaging Procedure Completed (mITT Population) (N = 230)
Largest dimension of tumor in main specimen (cm)	

Characteristics	Total LUM Imaging Procedure Completed (mITT Population) (N = 230)
Mean ± SD (N)	1.8±1.5 (171)
Median (Q1, Q3)	1.5 (0.9,2.0)
Range (min, max)	(0.0,10.9)
Tumor histology (biopsy and/or main lumpectomy specimen)[1]	
DCIS Only	43 (18.7%)
IDC +/- DCIS	160 69.6%
ILC +/- DCIS	25 (10.9%)
IDC + ILC	2 (0.9%
ER (+)[1]	209 91.7%
PR (+)[1]	176 79.6%
HER2 (+)[1]	18 (9.8%
Triple negative	
Yes	10 (4.3)
No	219 (95.2)
Unknown	1 (0.4)
At least one LN (+)	28 (15.2%)
All LN (-)	156 84.8%
No LN Biopsy	46 (20.0%)

I. Safety Results

Safety: A total of 234 patients were included in the safety analysis population. Overall, 214 patients (91.5%) reported chromaturia (blue-green discoloration of the urine) due to the blue color of the LUMISIGHT injection. In addition to the chromaturia events, 57 AEs observed in 39 patients were reported with four AEs related to the LUMISIGHT treatment Table 18. One serious AE of anaphylaxis was observed during the administration of LUMISIGHT; no deaths or UADEs were reported.

Table 18. Summary of Adverse Events by Severity and Relatedness to LUMISIGHT Treatment (Safety Population)

Severity	All			Mild			Moderate			Severe		Life Threatening	
Adverse Events	**All n (%)**	**Not Related n (%)**	**Related n (%)**	**All n (%)**	**Not Related n (%)**	**Related n (%)**	**All n (%)**	**Not Related n (%)**	**Related n (%)**	**All n (%)**	**Related n (%)**	**All n (%)**	**Related n (%)**
All AE events	271	53	218	255	41	214	14	12	2	1	1	1	1
Chromaturia	214	0	214	214	0	214	0	0	0	0	0	0	0
Other AEs	57	53	4	41	41	0	14	12	2	1	1	1	1
All patients with any AEs	215 (91.9%	33 (14.1%	214 (91.5%	214 (91.5%	25 (10.7%	214 (91.5%	12 5.1%	10 4.3%	2 0.9%	1 0.4%	1 0.4%	1 (0.4%)	1 (0.4%)
All patients with chromaturia	214 (91.5%	0	214 (91.5%	214 (91.5%	0	214 (91.5%	0	0	0	0	0	0	0
All patients with Other AEs	36 (15.4%	33 (14.1%	3 (1.3%)	25 (10.7%	25 (10.7%	0	12 5.1%	10 4.3%	2 0.9%	1 0.4%	1 0.4%	1 (0.4%)	1 0.4%

Abbreviation: AE = adverse event

J. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The Phase C Feasibility Study included 38 investigators listed on FDA Form 1572. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

K. Safety Conclusions

Safety: No adverse device effects were observed in this study.

The imaging agent, LUMISIGHT, was generally well tolerated by study subjects. No deaths were reported. One serious adverse reaction of anaphylaxis was observed – the subject was treated and recovered and then proceeded to receive standard of care lumpectomy (no imaging with the Lumicell DVS). No allergic reactions were observed in the 230 subjects that were enrolled in the study after the exclusion criteria modification. Most subjects experienced the AE of chromaturia (blue-green urine discoloration) which was expected based on the blue color of the LUMISIGHT imaging agent. The other events experienced by the study subjects were expected based on their underlying disease, change in medications, or were otherwise expected due to the subject undergoing and recovering from surgery.

2. Pooled Analyses of Safety in the Clinical Studies Evaluated

An analysis of pooled safety data was performed in 709 patients with breast cancer, 56 patients with other solid tumors, and 32 healthy patients (24 of whom received LUMISIGHT). Safety risks include serious AEs related to LUMISIGHT such as anaphylactic reactions across the evaluable safety populations 0.5%, 4 out of 765 subjects). Thus, a total of 789 patients were exposed to LUMISIGHT, 765 of whom were patients with cancer. The Pivotal Study included a total of 406 patients (53.1% of the evaluable safety population).

Summary data are presented in two groupings of patients who received LUMISIGHT:

- **Breast Cancer Safety Population**: All patients with breast cancer who participated in the Phase 1 IND study (N = 3), IDE feasibility studies Phase A (N = 10), B (N = 45) and C (N = 234), the IDE Pivotal Study (N = 406), and the study in patients receiving neoadjuvant therapy (N = 11), for a total of 709 patients with breast cancer.
- **Overall Safety Population**: All patients in the Breast Cancer Safety Population and the safety populations enrolled in non-breast cancer clinical trials (total of 765 patients).

In an analysis of AEs in the Breast Cancer Population and Overall Safety Population, chromaturia was the most frequently reported AE with 644 of 765 patients (84.2%) in the Overall Safety Population experiencing this expected event, whereas a quarter of patients (191 of 765 [25.0%]) had an AE other than chromaturia (Table 19).

There were no deaths. Life-threatening AEs (2 of 765 patients [0.3%]), SAEs (8 of 765 patients [1.0%]), and AEs leading to discontinuation (8 of 765 patients [1.0%]) were reported infrequently in the Overall Safety Population (Table 19).

Table 19. Overview of Adverse Events in the Breast Cancer and Overall Safety Populations

Category	Breast Cancer Safety Population (N = 709) LUMISIGHT Treatment Level (mg/kg)				Overall Safety Population (N = 765) LUMISIGHT Treatment Level (mg/kg)			
	0.5 (N = 6)	1.0 (N = 667)	1.5 (N = 1)	Control[a] 1.0 (N = 35)	0.5 (N = 26)	1.0 (N = 690)	1.5 (N = 14)	Control[a] 1.0 (N = 35)
Total no. of AEs	2	848	2	41	34	884	23	41
Chromaturia	1	564	1	30	17	585	13	30
AEs other than chromaturia	1	284	1	11	17	299	10	11
No. of patients (n [%]) with:								
Chromaturia	1 (16.7%)	564 (84.6%)	1 (100.0%)	30 (85.7%)	17 (65.4%)	584 (84.6%)	13 (92.9%)	30 (85.7%)
Chromaturia that was expected	1 (16.7%)	564 (84.6%)	1 (100.0%)	30 (85.7%)	17 (65.4%)	584 (84.6%)	13 (92.9%)	30 (85.7%)
Chromaturia that was related[b]	1 (16.7%)	562 (84.3%)	1 (100.0%)	30 (85.7%)	17 (65.4%)	582 (84.3%)	13 (92.9%)	30 (85.7%)
AE other than chromaturia	1 (16.7%)	160 (24.0%)	1 (100.0%)	8 (22.9%)	12 (46.2%)	167 (24.2%)	4 (28.6%)	8 (22.9%)
Related AE other than chromaturia[a]	0	29 (4.3%)	0	0	0	29 (4.2%)	0	0
Unexpected AE other than chromaturia	0	151 (22.6%)	0	7 (20.0%)	6 (23.1%)	154 (22.3%)	2 (14.3%)	7 (20.0%)
Life-threatening AE	0	2 (0.3%)	0	0	0	2 (0.3%)	0	0
SAE	0	6 (0.9%)	0	0	2 (7.7%)	6 (0.9%)	0	0
AE leading to discontinuation	0	8 (1.2%)	0	0	0	8 (1.2%)	0	0
Death	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; DVS = Direct Visualization System; SAE = serious adverse event.
[a] related AE was defined as an AE whose relationship was probably or definitely related.
[b] Patients in the Control Arm received LUMISIGHT at a dose of 1.0 mg/kg but did not receive Lumicell DVS imaging.

3. Early Clinical Development: Phase 1 IND, IDE Feasibility Studies Phase A and Phase B

The initial Phase 1 IND Study (DUK1-12-137; n = 15) was designed to establish baseline safety and initial ex-vivo imaging of cancer and normal tissue, and to determine the safe and recommended dose of LUMISIGHT and injection timepoint relative to surgery.

The initial Phase 1 IND Study was followed by a series of two IDE feasibility studies, termed Phase A and Phase B.

- Phase A - Study LUM-015/2.6-001; n = 15 (5 subjects were not injected with LUMISIGHT to measure tissue background signal, and 10 subjects were injected with LUMISIGHT). With this study, the dose of 1.0 mg/kg and the imaging timepoint of 2-6 hours after injection of LUMISIGHT were determined.

- Phase B - Study LUM-015/2.6-001; n = 45. The study was designed to collect pathology and imaging data to develop Lumicell's initial patient calibration tumor detection software, and to understand how surgeons would use the device. The resulting developed patient calibrated tumor detection software was then used and refined during the Feasibility Phase C Study CL0006.

No serious adverse events related to LUMISIGHT were reported in these studies.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

In accordance with the provisions of section 515(c)(3) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

The parallel NDA 214511 for LUMISIGHT (pegulicianine) was reviewed by the Medical Imaging Drug Advisory Committee (MIDAC) at an advisory meeting held on March 5, 2024. Among the MIDAC panel 16 members voted that the benefits of the drug outweigh its risks and 2 members voted that the benefits of the drug do not outweigh the risks, there was 1 abstention.

B. FDA's Post-Panel Action

NO PMA POST-PANEL ACTION APPLICABLE; PLEASE SEE NDA 214511 FOR RELEVANT DRUG ACTIONS.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The evaluation of effectiveness of the LUMISIGHT and Lumicell DVS combination product as an adjunct to SoC BCS was based on the analysis of the effectiveness endpoints results in the Pivotal Study CL0007.

For the Pivotal Study CL0007, the effectiveness results demonstrated success in detecting residual cancer during *in vivo* examination of the lumpectomy cavity and guiding the removal of cancerous tissue that would have otherwise remained undetected after SoC BCS in 27 out of 357 patients (7.6%; 95% CI: 5.0%, 10.8%).

The tissue-level sensitivity was 49.1% (95% CI: 36.4%, 61.9%; GEE Estimator), but did not meet the pre-specified criterion of having a lower bound of the 95% CI greater than 40%. The tissue-level specificity was 86.5% (95% CI: 84.5%, 88.3%; GEE Estimator), and did meet the prespecified criterion of having the lower bound of the 95% CI greater than 60%.

Use of the combination product converted 15% of patients with positive margins after SoC BCS to negative margins, potentially sparing 8 patients from a subsequent surgery to remove residual cancer.

Analyses of effectiveness endpoints in Pivotal Study CL0007 provided additional effectiveness results, as follows:

- 9 out of 62 (14.5%) patients with pathology-positive margins after SoC BCS were converted to having pathology-negative margins after additional Lumicell DVS guided shaves, indicating a potential to reduce the rate of second surgeries due to positive margins
- 19 out of 357 (5.3%) patients had negative margins after SoC BCS, but had residual cancer found in at least one LUM-guided shave; that is, 19 patients would have completed their initial SoC procedure with cancer remaining in the lumpectomy cavity and likely would not have received a second surgery because the SoC margins were assessed as negative

The pivotal study demonstrated that the combination product (LUMISIGHT and Lumicell DVS) successfully provides an *in vivo* image of the lumpectomy cavity to the breast cancer surgeon which allows the surgeon to detect and remove more cancerous tissue than SoC BCS alone. Thus, LUMISIGHT and the Lumicell DVS, together with SoC BCS, can provide removal of additional cancer and a meaningful surgical intervention with demonstrable clinical benefits compared with SoC surgical intervention only.

B. Safety Conclusions

No UADEs were reported in Pivotal Study or in the Overall Safety Population; no device issues resulted in any AEs. The safety profile of LUMISIGHT was characterized in clinical studies that enrolled a total of 726 patients (703 with breast cancer) administered a single 1 mg/kg dose of LUMISIGHT.

- The expected AE of chromaturia was the most frequently reported AE, occurring in 85% of

patients.

- Across the clinical studies, there were no deaths, and life-threatening AEs (0.3%), SAEs (1.1%), and AEs leading to discontinuation (1.0%) were reported infrequently.
- 85% of AEs were mild in severity and resolved without sequelae.
- A 1.4% rate of hypersensitivity was observed after LUMISIGHT injection. This includes a 0.6% anaphylaxis rate (4/726 patients). This risk can be mitigated by appropriate warnings and immediate access to appropriate interventions.

C. Benefit-Risk Determination

Benefits

The LUMISIGHT and Lumicell DVS combination product is the first system introduced in a clinical setting that is designed for *in vivo* imaging of the lumpectomy cavity for intraoperative detection of residual cancer after SoC BCS. Clinically meaningful benefits were observed for patients based on the evaluation of safety and effectiveness results across the clinical development program. The clinical benefits were shown to include facilitating a more complete resection than SoC surgery alone that can potentially lead to reduction of re-excision surgeries, and the associated impact on patients and healthcare resources and costs.

Improvements Over Standard of Care Breast-Conserving Surgery

- As an adjunct to SoC surgery, some patients received an improved surgical procedure with LUMISIGHT and the Lumicell DVS combination product as demonstrated by the results of the primary effectiveness endpoint, removal of residual cancer, in the Pivotal Study.
- The system operates in real-time with cancer detection and image-guided shave information visualized within the lumpectomy cavity. This approach provides an advantage for some patients when used adjunctively with SoC, because routine SoC methods are typically limited to *ex vivo* tissue examination several days after the initial surgery.
- LUM-guided shaves can remove more cancerous tissue that can help achieve a more complete resection and probably lessen the need for second surgeries as well as reduce pathology laboratory resources associated with those repeat surgeries. Furthermore, by potentially avoiding the need for second surgeries, the rate of possible complications and morbidities associated with second surgeries, e.g., pain; poorer cosmetic outcomes; and inherent risks of an additional surgery, such as anesthesia effects, infection, post-surgery trauma, patient anxiety, would be reduced and the patient may progress into postsurgical treatment sooner (Metcalfe, et al. 2017).
- Use of the system may reduce the need for radiation therapy in patients 70 years of age or older and ER-positive, for whom adjuvant radiation may have been omitted according to the American Society for Radiation Oncology (ASTRO) evidence-based guidelines.

Ease of Implementation into Existing Patient Management and Surgical Workflow

- Injection of a single IV dose of LUMISIGHT 2-6 hours prior to surgery conforms to current patient management of surgical procedures. Other than preparation of LUMISIGHT by the Pharmacy, no additional patient preparation is required for administration of the imaging agent.
- The use of the combination product as an adjunct to SoC BCS has minimal impact on current surgical protocols, as the surgeon would routinely perform the SoC procedure (e.g., selective or comprehensive shaves) first and then introduce the combination product within operative workflows. The imaging procedure using the Lumicell DVS only adds several minutes to the procedure (Lanahan et al. 2021) Some dyes used in lymphatic mapping procedures can interfere with LUMISIGHT and should not be administered prior to LUMISIGHT imaging.

Detection and Removal of Residual Cancer

- Overall, more cancerous tissue was detected and surgically removed by using the combination product.

Impact on Positive Margin Rates and Second Surgeries

- Without the use of the LUMISIGHT and Lumicell DVS combination product, 19 patients in the Pivotal Study would have completed their initial surgical procedure with cancer remaining in the lumpectomy cavity and likely would not have received a second surgery because the SoC margins were assessed as negative.
- In the Pivotal Study, it was also shown that by removing LUM-guided shaves, two patients were converted from negative SoC margins to final positive margins. Even though these patients had to go through a second procedure, the finding of cancer in the LUM-guided shave prompted more cancer to be removed from these patients that otherwise would have not been surgically addressed.

Impact on Patients

- Current treatment practices for patients with breast cancer who have positive lumpectomy margins often involve lengthy medical, surgical, and radiotherapeutic regimens that may cause high anxiety, emotional distress and uncertainty (Baqutayan et al. 2012, Maass et al. 2015, Kim et al. 2020). Additionally, patients undergoing a second surgery due to positive margins have a 48.0% higher likelihood of experiencing at least one complication, and the likelihood of having multiple complications (e.g., infection, hematoma, severe breast pain, wound necrosis) is estimated to be 89.0% higher than patients undergoing a single SoC lumpectomy (Metcalfe et al. 2017).
- Furthermore, as part of the SoC treatment for breast cancer, most patients undergo adjuvant radiation therapy even when the patient has negative margins, because it reduces the rate of local recurrence when compared to SoC BCS alone (Fisher et al. 2002, Veronesi et al. 2002). By targeting and guiding the removal of cancerous tissue detected by LUMISIGHT, some

patients could become candidates to be spared radiation therapy, which introduces additional comorbidities and detrimental side effects. Guidelines currently exist for patients with negative lumpectomy margins who are over 70 years and estrogen receptor (ER) positive (Smith BD et al. 2018) to be spared radiation, and clinical trials are underway to further investigate patients that could be spared radiation. Additionally, by detecting residual cancer compared to SoC BCS alone, some patients may become candidates to benefit from radiation therapy who may have not received radiation therapy were it not for detection of the additional cancer.

Impact on Cosmesis

- As shown in the effectiveness results of the Pivotal Study, removal of residual cancer assisted by the LUMISIGHT and Lumicell DVS combination product leads to, on average across the entire study population, one LUM-guided shave, which had minimal impact on cosmesis. For patients with at least one LUM-guided shave removed, the additional tissue represented approximately 20.0% of total tissue volume removed. Other studies have shown that in patients who had comprehensive surgical shaves, no impact was found on postoperative complications or on patient's perception of their cosmetic outcomes when tissue volume was approximately 30.0% (Chagpar et al. 2015, Dupont et al. 2021).
- Patients with cancerous tissue detected and removed during initial surgery can potentially avoid second surgeries and the poorer cosmetic outcomes associated with them.

Impact on Healthcare Burden and Resources

- Patients with breast cancer may undergo numerous medical and surgical procedures that involve significant healthcare resource time and expenditure. Healthcare systems routinely performing serial SoC surgeries on breast cancer patients may increase the burden in healthcare when patients receive a re-excision surgery.
- By providing additional information during the initial surgery, use of the LUMISIGHT and Lumicell DVS combination product can potentially reduce the rate of second surgeries, thereby reducing overall surgical time.
- A retrospective analysis of approximately 290,000 patients undergoing BCS demonstrated that surgeons who performed fewer BCS tend to have higher rates of second surgeries (Kaczmarski 2019). The Pivotal Study was conducted at high-volume, metropolitan breast cancer centers with highly experienced surgeons.
- Overall, LUMISIGHT and the Lumicell DVS combination product provides an adjunctive surgical option to detect and remove cancer not detected by SoC BCS in some patients.

Risks

The potential risks include:

- Anaphylaxis and Other Serious Hypersensitivity Reactions

A 0.6% anaphylaxis risk (4/726 patients) has been reported following administration of LUMISIGHT.

- Risk of Misinterpretation of Imaging Results

False positive and false negative findings may occur during use of LUMISIGHT to detect residual cancer. False positives can lead to unnecessary tissue removal. Absence of signal in the lumpectomy cavity does not rule out the presence of residual cancer. As the LUM product is used as an adjunct to SoC, a false negative result is no worse than SoC.

- Potential Interference from Dyes Used for Sentinel Lymph Node Mapping

Blue dyes used for sentinel lymph node (SLN) mapping procedures interfere with LUMISIGHT. The potential of other dyes to interfere with LUMISIGHT imaging has not been evaluated. Avoid administration of dyes used for SLN mapping procedures before imaging the lumpectomy cavity in patients receiving LUMISIGHT.

Benefit-Risk Assessment

Lumicell's assessment of benefit-risk involved a comprehensive analysis of the safety and effectiveness data from the Pivotal Study, and additional relevant data from other clinical and nonclinical studies in the development program for LUMISIGHT and the Lumicell DVS combination product.

The combination product in the Pivotal Study demonstrated success in detecting and guiding the removal of residual cancer in 27 patients that would have otherwise remained undetected after SoC BCS. Additionally, 14.5% of patients with pathology positive margins after SoC BCS were converted to final negative margins by removing a Lumicell DVS-guided shave and thereby saving a potential second surgery. In the Pivotal Study, 7.0% of patients had additional cancer removed that was undetected during the initial SoC surgery. Moreover, in the Pivotal Study, in approximately 49.0% of patients (176 out of 357 patients), the combination product confirmed either no residual cancer was present or a negative margin outcome. Results from the Pivotal Study also show that in 41 patients with residual cancer removed, 27 had a more complete resection guided using LUMISIGHT, with 20 of those 27 patients having residual cancer only found by the Lumicell DVS. Although the sensitivity endpoint of the Pivotal study was not met, the limitations of sensitivity were counterbalanced by improvements over SoC margin detection rates, such that the totality of information supports clinically meaningful benefit of the device. The combination product benefits are provided by a real-time intraoperative cavity assessment modality for surgeons to achieve a more complete cancer resection in some patients, hence surgically facilitating conversion from positive to negative margins, as well as overall potential positive impact on patient well-being, cosmesis, disease burden, and healthcare resources.

No device related adverse events were reported across the clinical study program. Furthermore, the relatively low frequency of SAEs and no reported UADEs during the clinical study program contributes to the overall favorable safety profile of the combination product in the breast cancer population. The main identifiable residual risk is the potential for anaphylaxis to the optical imaging agent LUMISIGHT. To mitigate this risk, the Prescribing Information for LUMISIGHT (see Appendix) indicates to always have emergency resuscitation equipment and trained personnel available. Also, if a hypersensitivity reaction is suspected, interrupt the injection of LUMISIGHT. To further mitigate any potential adverse reactions or device events, several warnings on the proposed label were included.

LUMISIGHT is administered in pre-operative settings where patients are monitored and treated by trained personnel with intervention protocols. No deaths were observed in the pre-market clinical testing. The MIDAC Panel agreed that risk mitigations including clear labeling, training, a post-market pharmacovigilance program to monitor drug safety, and a Device Complaints Management process are reasonable to manage adverse reactions.

In summary, LUMISIGHT and the Lumicell DVS combination product demonstrated an ability to facilitate removing residual cancer that remains undetected in some patients with breast cancer after SoC BCS. The potential for anaphylaxis to the optical imaging agent LUMISIGHT is a residual risk that is adequately mitigated and outweighed by the significant benefits of the product.

Patient Perspective

During the Pivotal Study, Patient Reported Outcome Measures (PROMs) were collected as an exploratory endpoint using a module of the BREAST-Q survey. This is a rigorously developed and validated PROM survey designed to evaluate outcomes among women undergoing different types of breast surgery from the patient perspective. The “Satisfaction with Breast” survey was used. Participation in the PROM survey was an optional aspect of the Pivotal Study; therefore, this part of the study was not statistically powered. The surveys were completed before surgery and at three time points after surgery: during routine follow up, 3-months and 6 months after surgery. The analysis of the data included comparison of survey responses between patients with no LUM-guided shaves removed and those with at least one LUM-guided shave removed.

For this exploratory analysis, the PROM data collected showed that the majority of the patients responded either “Very Satisfied” or “Somewhat Satisfied” across all the timeframes pre- or post-surgery.

In addition, PROM responses to each question were generally similar between those patients with or without LUM-guided shaves for each PROM time frame. No statistically significant difference between the patient overall satisfaction across the two groups was observed. However, the study was not powered to detect a difference between these groups.

As the questionnaire only had 3 questions asked in the same way before and after the surgery, the distribution of the changes of the patient responses post-surgery from the pre-surgery was only examined on these 3 pairs of the data. The distributions of responses look similar across the timeframes post-surgery.

D. Overall Conclusions

The data in this application supports a reasonable assurance of safety and effectiveness of the LUMISIGHT and Lumicell DVS combination product when used in accordance with the indications for use.

The benefit-risk assessment supports the proposed indication of the combination product in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

XIV. CDRH DECISION

CDRH issued an approval order on April 17, 2024.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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XVII. APPENDIX

1. Final Prescribing Information (PI) for LUMISIGHT (pegulicianine) for Injection, Prescribing Information (PI) submitted to NDA 214511