LUMISIGHT (PEGULICIANINE) FOR INJECTION

SPONSOR BRIEFING DOCUMENT

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE
MEETING DATE: MARCH 5, 2024

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

1 TABLE OF CONTENTS

1.1 List of Tables

1.2 List of Figures

1.3 List of Abbreviations

Abbreviation	Definition
AE	Adverse events
AUC	Area under curve
BCS	Breast conserving surgery, also referred to as lumpectomy
BMI	Body mass index
CDER	Center for Drug Evaluation and Research at the FDA
CDRH	Center for Devices and Radiological Health at the FDA
CI	Confidence interval
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DDI	Drug-drug interactions
DVS	Direct Visualization System
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
ICF	Informed consent form
ICH	International Council for Harmonisation
IDC	Invasive ductal carcinoma
IDE	Investigational Device Exemption
ILC	Invasive lobular carcinoma
IND	Investigational New Drug
IV	Intravenous
LL	Lower limit
LLT	Lowest level term
Lumicell DVS	Lumicell Direct Visualization System
LUM System	LUMISIGHT and the Lumicell DVS combination product
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteases
N	Normal tissue
NCI	National Cancer Institute
NDA	New Drug Application
OBS	Oncoplastic breast surgery

Abbreviation	Definition
PD	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics
PMA	Pre-market approval
PROM	Patient-reported outcomes measure
PT	Preferred Term
ROC	Receiver operating characteristics
SAE	Serious adverse events
SLN	Sentinel lymph nodes
SoC	Standard of care
SoE	Schedule of Events
T	Tumor
US	United States

2 EXECUTIVE SUMMARY

2.1 Introduction

Lumicell is seeking marketing approval for a combination product consisting of LUMISIGHT (pegulicianine) for injection - an optical imaging agent, and the Lumicell Direct Visualization System (DVS) - a novel, real-time, intracavity fluorescence-guided imaging technology. The system is intended for use as an adjunct to standard of care (SoC) breast conserving surgery (BCS) in adults with breast cancer for the intraoperative detection of residual cancerous tissue within the resection cavity. The use of the combination product can also help achieve final negative margins, allowing the patient to potentially avoid the need for a follow-up surgery and move more efficiently into the next stage of care.

LUMISIGHT is currently being reviewed by the Center for Drug Evaluation and Research (CDER) under a New Drug Application (NDA) and the Lumicell DVS is being reviewed by the Center for Devices and Radiological Health (CDRH) under a Pre-market Approval (PMA) application.

For simplicity, the LUMISIGHT and Lumicell DVS combination product is referred to as the LUM System throughout this document.

The current limitations of SoC lumpectomy, along with imperfect margin pathology, make it insufficient to find residual cancer in the cavity. This often leads to the need for follow-up surgeries, wide-spread use of adjuvant therapies (and their associated comorbidities), and in some cases, local cancer recurrence.

When used as an adjunct to SoC, the LUM System enables surgeons to find and remove residual cancer left behind with no significant impact to cosmesis, resulting in a more complete cancer resection and a reduction in second surgeries.

Overall, the benefits of real-time assessment of the lumpectomy cavity and removal of residual cancer in patients with breast cancer outweigh any potential risk of anaphylaxis, which can be managed in the pre-operative hospital setting and through appropriate labeling.

2.2 Background and Unmet Need

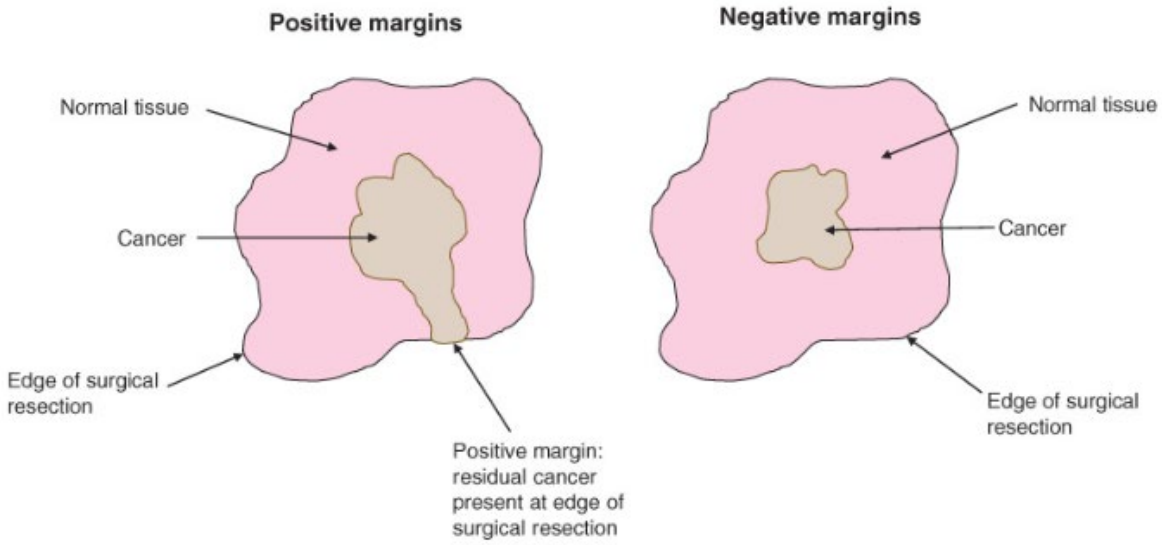
Breast cancer is both a life threatening and irreversibly debilitating disease and remains the most common cancer in women. Approximately 300,000 women were estimated to have newly diagnosed breast cancer in the United States (US) in 2023, with an additional 43,700 deaths.[1,2] Over their lifetime, 1 in 8 women will be diagnosed with breast cancer.[1]

For most patients diagnosed with early-stage breast cancer, their primary treatment is surgery: either a mastectomy (removal of the entire breast) or a lumpectomy, also termed BCS. The goal of a lumpectomy is to remove as much cancer as possible, while sparing normal breast tissue to improve cosmetic outcomes (see Figure 4 for a SoC lumpectomy description). Studies show that a lumpectomy followed by radiation therapy provides the same survival as mastectomy for most women with breast cancer.[6] Over 60% of all patients

(or about 200,000) with early-stage breast cancer undergo BCS as part of their treatment. Lumpectomy with negative margins followed by radiation and systemic therapy provides excellent local control, however some breast cancer patients still develop local recurrences, often near the site of the primary tumor.[3–5] Studies assessing 10-year recurrence rates of lumpectomies following radiotherapy range from 2% to 19.3%.[6–9] Further studies demonstrate that incomplete tumor resection, as represented by positive margins, doubles the risk of recurrence,[10] ultimately leading to 1 excess death for every 4 breast cancer local recurrences.[11]

The effectiveness of BCS relies on excising the entire tumor at the time of lumpectomy. However, the completeness of tumor excision is difficult to ascertain at the time of surgery, and the extent of potential residual disease is not determined until final pathology assessment is completed, which can be a week or more after the initial surgery (Figure 1). If positive margins are identified by pathology, which occur in 10-36% of the patients,[13,14] a follow-up surgical procedure is typically required to re-excise additional breast tissue at that site to ensure that all gross tumor is removed. These follow-up surgeries result in significant burden to the patient and the healthcare system and create delays in post-surgery treatment.

Figure 1: Margin Assessment of Lumpectomy Specimen



Schematic of margin assessment of lumpectomy specimen, comparing positive (left panel) to negative (right panel) margins. Identification of positive margins on the lumpectomy specimen will commonly result in additional surgery.[15]

Current perioperative techniques approved by the Food and Drug Administration (FDA) to identify residual tumor or positive margins all rely on *ex vivo* (i.e., outside the body) specimen analysis and technologies, such as radiofrequency spectroscopy (Margin Probe),[17] intraoperative X-ray (e.g., Faxitron),[18] and optical coherence tomography (Perimeter OCT).[19] All of these attempt to predict the margin status, visualize the tumor

within the excised specimen, or visualize the margin itself. None directly assesses the presence of residual cancer in the surgical cavity.

Routine pathology assessment, as part of the current SoC BCS, has well-known limitations and challenges:

- Excised breast specimens deform immediately after excision, causing surgeons and pathologists to lose specimen surface orientation relative to the lumpectomy cavity where tumor may remain.
- Handling and sectioning of specimens can expose tumor not actually at the margin but nevertheless attributed to the margin.
- Given the time, cost, and complexity of sectioning excised tissue, pathologists are only able to examine < 1% of the lump's surface area.[20]
- Margin assessment is designed to find cancer that is connected to the original lumpectomy specimen but is ill-suited to identify noncontiguous lesions.
- Routine pathology assessment of excised tissue can take days or even weeks, delaying further treatment for the patient.

These factors limit the ability to predict the presence of residual disease in the patient. In a study where additional cavity shaves were removed after the main specimen resection, and when a margin was declared positive in the main specimen, results showed that 65% of the time no tumor was found in the subsequent shave.[16] Conversely, 19% of the time in which a negative margin from the main specimen was determined, the cavity shave contained tumor. Therefore, this residual cancer left behind in the cavity of the patient would not have been identified by pathology assessment of the main specimen and would have not led to follow-up surgery. Thus, lumpectomy specimen margins are not always reliable in predicting residual disease in BCS.[16]

Currently, there is no FDA-approved intraoperative technology available that directly examines the lumpectomy cavity for residual cancer after the main specimen is removed in SoC BCS. Hence, an intracavity product as an adjunct to surgical intervention is needed to enable surgeons to achieve a more complete breast cancer resection.

2.3 Product Description

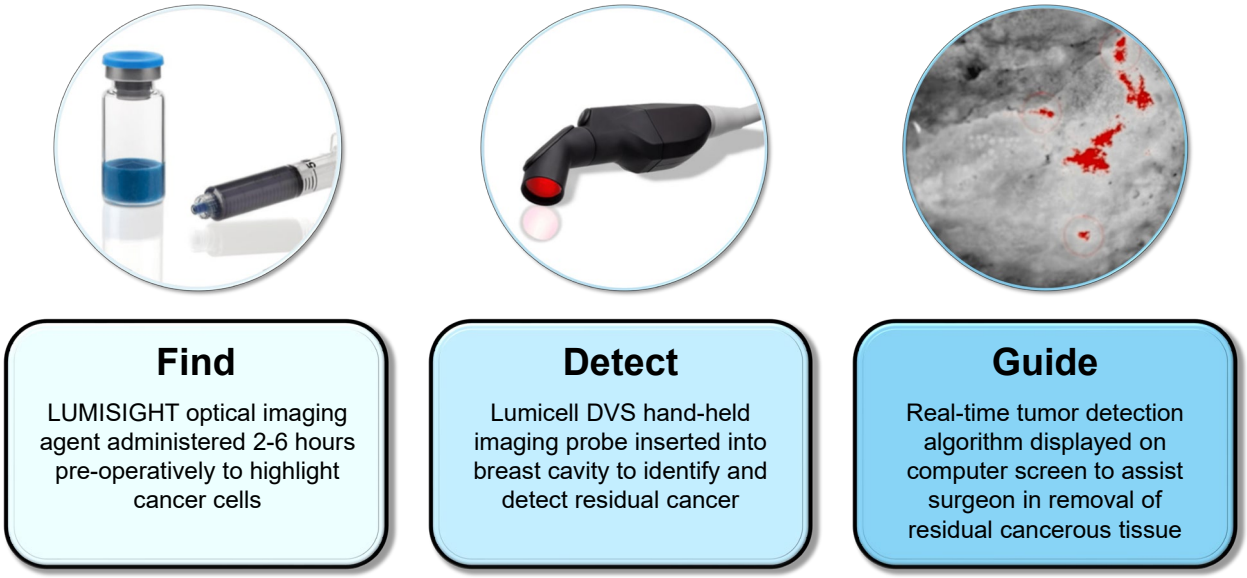
The LUMISIGHT Optical Imaging Agent and Lumicell DVS were developed to fill this important need. The system is designed to detect residual cancer after the main specimen has been removed, leaving a relatively low prevalence of small cancer embedded in normal tissue.

The LUM System is a novel, real-time, fluorescence-guided, intracavity imaging technology that enables detection and resection of residual cancer not removed during SoC BCS (Figure 2). LUMISIGHT (Figure 6) is optically inactive (not emitting fluorescence) when manufactured because the close proximity of the fluorescent quencher to the fluorescence dye prevents fluorescence emission from the dye to escape. After intravenous (IV) injection,

LUMISIGHT reaches the tumor and its immediate surrounding areas, where it gets cleaved by cathepsins[24] and matrix metalloproteases (MMP). These enzymes have higher levels of activity in and around tumor cells, as well as in tumor associated cells, as compared to normal tissue.[25] After cleavage, the quencher separates from the fluorescent dye and allows cancerous tissue and its invasive front to fluoresce.

The Lumicell DVS is intended to be used after the SoC lumpectomy is completed. The surgeon inserts the Lumicell DVS handheld probe into the lumpectomy cavity and scans its surface, generating images that are analyzed by the tumor detection algorithm and displayed in real-time to the surgeon on a computer screen. Regions suspected to contain residual cancer are highlighted on the screen to assist the surgeon in visualizing where additional tissue should be removed.

Figure 2: LUMISIGHT and Lumicell DVS – Fluorescence-Guided Intracavity Imaging Technology



DVS: Direct Visualization System

The proposed indication for LUMISIGHT and Lumicell DVS is 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 (also known as BCS).

2.4 Development Program

The LUM System clinical development program in breast cancer consists of 6 studies in more than 700 patients and an additional cardiovascular safety study in healthy volunteers (Table 5). Efficacy supporting the use of the LUM System in breast cancer comes from Pivotal Study CL0007. The safety of the combination product is supported by the 6 breast cancer studies (703 patients) and 2 studies in other cancers (23 patients). Section 5.2 describes in detail the clinical development program.

2.4.1 Pivotal Study: CL0007

The Pivotal Study (CL0007) was a multicenter, two-arm, randomized, blinded trial enrolling 406 patients injected with LUMISIGHT at 1 mg/kg. The study was designed to evaluate the safety and efficacy of LUMISIGHT and the Lumicell DVS to detect residual cancer in the cavity as an adjunct to SoC BCS. Randomization after SoC BCS was intended to minimize potential surgeon bias. Thus, the study was not powered to detect differences between treatment and control arms.

This study recruited breast cancer patients from 14 medical centers, 10 academic-affiliated institutions, and 4 non-academic hospitals throughout the United States, representing a diverse geographical distribution of enrolled patients and surgeons.

Patients in this study were female, 18 years of age or older, and had histologically or cytologically confirmed primary invasive breast cancer, ductal carcinoma in situ (DCIS), or primary invasive breast cancer with a DCIS component. The methods for obtaining the histological samples included core needle biopsies or fine needle biopsies. Patients who had diagnostic open surgical biopsies were excluded from participation. Patients must have also been scheduled for a lumpectomy procedure and able and willing to follow study procedures and instructions.

Patients who were excluded from the study at screening had a diagnosis of bilateral breast cancer and were undergoing a bilateral resection procedure, had received an investigational drug within 30 days of enrollment, were pregnant at the time of diagnosis of their breast cancer, or were unwilling to use 2 medically acceptable forms of contraception if sexually active on entering the study and for 60 days after injection. Importantly, patients who planned to have administration of blue dyes for sentinel lymph node mapping prior to imaging with the Lumicell DVS were also excluded from the study. However, administration in the cavity of blue dyes after imaging with Lumicell DVS was allowed (see Section 7.1.1.4.2 for more details).[26]

Full lists of the inclusion and exclusion criteria of this study are provided in Appendix 12.2 and Appendix 12.3, respectively.

A summary of the study procedures is below.

All eligible patients with breast cancer were injected with 1 mg/kg of LUMISIGHT 2-6 hours prior to surgery (see Section 6.3 for details on selection of this dose and regimen).

- Surgeons performed their SoC lumpectomy blinded to the patient's study arm, which may include *ex vivo* X-ray imaging of the main specimen and removal of SoC shaves, when needed (see Section 3.2 for description of current SoC procedures).
- Once the surgeon declared that the SoC procedure was completed, the patient was then randomized 10-to-1, to undergo LUM-guided imaging (treatment arm) or no LUM-guided imaging (control arm). Randomization was implemented to minimize potential surgeon bias, that is, to ensure surgeons perform their SoC procedure without reliance on the LUM System to identify areas suspected to contain residual

cancer; thus the study was not powered to detect differences between treatment and control arms (see Section 7.1.1.2 for more details and justification of the 10:1 randomization ratio).

  - Patients randomized to the treatment arm had their lumpectomy cavity scanned with the Lumicell DVS and when indicated by the tumor detection algorithm, LUM-guided shaves were removed. The process was repeated until no LUM-positive signals were obtained; however, no more than 2 LUM-guided shaves were allowed to be removed from a single cavity orientation. Patients in the treatment arm were able to serve as their own control to evaluate surgical outcomes because tissue samples were collected during the SoC procedure and then during the LUM-guided procedure.
  - Patients randomized to the control arm did not undergo imaging with the Lumicell DVS and are not included in the efficacy analysis, but are included in the safety analysis.

- All tissues removed were sent to pathology for standard tumor assessments and margin evaluation.
  - To mitigate potential bias in the pathology assessment of the specimens, through a clinical protocol specified tissue naming convention, pathologists were blinded to whether the tissue being evaluated was removed as part of the SoC lumpectomy or the LUM-guided intervention.
- Approximately 1 week after the lumpectomy procedure, the sites issued their standard pathology report and data was entered into the patient's case report form (CRF) (see Section 7 for efficacy results).
- Patients were followed for safety until the first post-surgery visit to their treating physician (see Section 8 for safety results).

Pivotal Study CL0007 included 3 co-primary efficacy endpoints, and several clinically meaningful secondary endpoints.

2.4.1.1 Co-Primary Endpoints and Performance Goals Selection

Prior studies have shown that local recurrences often occur close to the original tumor site with histological characteristics similar to the primary tumor, implying that local recurrences may arise from residual cancer left behind during the initial SoC lumpectomy.[3] Thus, the LUM System is designed to identify residual cancer in the lumpectomy cavity after the SoC procedure. Further, the design of LUMISIGHT, which is activated not only by the tumor but also by tumor associated cells surrounding the primary site, assists in removing the tumor with some additional non-tumor tissue and allows for the conversion of positive margins to negative margins.

As the goal of lumpectomy is a complete cancer resection, removing residual cancer left behind during the SoC procedure may benefit patients in the long term. Thus, the surrogate co-primary endpoint of removal of residual cancer was selected and defined as:

- Removal of Residual Cancer: the percent of patients who had residual cancer found in at least 1 LUM-guided shave among all patients in the treatment arm. Residual cancer was defined as tumor found by pathology in a LUM-guided shave after the SoC lumpectomy is completed; that is, tumor that current SoC lumpectomy failed to remove.

A performance goal for the lower bound of the 95% confidence interval (CI) of **> 3%** was selected for this endpoint based on estimates of local recurrence as described in Section 7.1.2.1. This performance goal was agreed to by the FDA.

To achieve the performance goal above, the LUM System must balance removing as much cancer as possible while sparing non-cancerous tissue. This trade-off is determined by the tissue-level sensitivity and specificity. Thus, 2 additional co-primary endpoints were evaluated in the Pivotal Study:

- Tissue-Level Diagnostics: these endpoints measure the ability for each of the images collected with the LUM System to correctly identify regions with or without residual cancer.
    - Tissue-Level Sensitivity: the percent of truth standard positives that produced a LUM-positive signal.
    - Tissue-Level Specificity: the percent of truth standard negatives that produced a LUM-negative signal.

The performance goals for these endpoints were based on Lumicell's prior feasibility study and agreed to by the FDA. For sensitivity, the lower bound of the 95% CI needed to be **> 40%** to meet the performance goal. For specificity, the lower bound of the 95% CI had to be **> 60%** to meet the performance goal. A detailed description for the selection of these performance goals and the evaluation of sensitivity and specificity is included in Section 7.1.2.2.

2.4.1.2 Clinically Meaningful Pre-Defined Secondary Efficacy Endpoints

In addition to the primary endpoints, several clinically meaningful secondary endpoints were also evaluated, including:

- Conversion of positive SoC margins to final negative margins by excising LUM-guided shaves (Section 7.1.8.1). This endpoint indicates the impact of the LUM System to reduce the rates of second surgeries due to positive margins.
- Average volume of LUM-guided shaves and contribution to total excision volume (Section 7.1.8.2). This endpoint indicates how much additional tissue is removed by using the LUM System; the impact of this added tissue volume to patient's cosmesis

is described in the patient surveys collected as an exploratory endpoint (Section 7.1.9.1).

- Patient-level sensitivity and specificity analyses (Section 7.1.8.3). This endpoint extrapolates the tissue-level diagnostic performance to a patient-level characterization.

The full list of all secondary endpoints is provided in Appendix 12.4.

2.4.1.3 Exploratory Endpoint

The following exploratory endpoint was also evaluated:

- Patient reported outcomes measures (PROMs) to evaluate patient's perceived breast satisfaction before and at 3 timepoints after surgery (Section 7.1.9.1).

2.5 Efficacy Findings

2.5.1 Co-Primary Efficacy Endpoints

The Pivotal Study met its co-primary endpoint of removal of residual cancer and tissue-level specificity but did not meet the lower bound of the confidence interval for tissue-level sensitivity significance (Table 1).

Table 1: Results from Co-Primary Endpoints

Co-Primary endpoint	Performance Goal for the Lower Bound of the CI	Results
Removal of residual cancer	> 3%	7.6% (27/357; 95% CI: 5.0%, 10.8%)
Tissue-level sensitivity	> 40%	49.1% (34/69; 95% CI: 36.4%, 61.9%)
Tissue-level specificity	> 60%	86.5% (1940/2277; 95% CI: 84.5%, 88.3%)

CI: Confidence interval

The LUM System detected residual cancer and guided the removal of the cancerous tissue that would have remained after SoC BCS in 27 (7.6%; 95% CI: 5.0%, 10.8%) patients, with the lower bound of the confidence interval above the pre-defined performance goal of 3%.

Of these 27 patients, 22 had residual cancer removed in LUM-guided shaves corresponding to negative margin orientations. Out of these 22, 19 had all negative margins after SoC BCS, that is, these 19 patients would have completed their initial SoC procedure with cancer remaining in the lumpectomy cavity and likely would have not received a follow-up surgery because the SoC margins were negative (Section 7.1.7.1) Hence, the combination of LUMISIGHT and the Lumicell DVS was highly beneficial to these patients in removing cancerous tissue and potentially reducing long-term local disease progression.

The sensitivity was 49.1% (95% CI: 36.4%, 61.9%), with the lower bound of the 95% confidence interval not meeting the preset performance goal of > 40%. The specificity was 86.5% (95% CI: 84.5%, 88.3%) and successfully met the performance goal of the lower bound of the confidence interval > 60%. The Youden Index was 0.36 (95% CI: 0.21, 0.50),

demonstrating that the system provides informed, non-random diagnosis for the presence or absence of residual cancer. Additional analyses show that the area under the curve (AUC) of the receiver operating characteristics (ROC) curve is 0.7, suggesting 70% likelihood of correctly classifying residual cancer present or not present in the lumpectomy cavity (AUC of 0.5 indicates a system that provides no discrimination, whereas an AUC of 1.0 indicates a perfect classification device) (see Section 7.1.7.2 and Figure 17 for details).

2.5.2 Clinically Meaningful Pre-Defined Secondary Efficacy Endpoints

Results of the clinically meaningful pre-defined secondary efficacy endpoints are summarized below.

2.5.2.1 Conversion of Positive SoC Margins to Final Negative Margins by Excising LUM-Guided Shaves

In the Pivotal Study, positive margins were defined as cancer cells present at the inked surface of the resected tissue for patients with invasive cancer with or without associated DCIS,[27] or less than 2 mm from the inked surface of the resected tissue for patients with pure DCIS.[10]

The percent of patients converted from positive margins after the SoC BCS to final negative margins by excising LUM-guided shaves was 14.5% (9 out of 62 patients; 95% CI: 6.9%, 25.8%; Table 2). In 8 out of these 9 patients, a second surgery was avoided, with 1 patient having a follow-up surgery even with final negative margins based on a tumor board decision; no cancer was found in that second surgery. Thus, these data indicate that follow-up surgeries can potentially be avoided by converting initial positive margins after the SoC procedure to negative margins by excising LUM-guided shaves.

Table 2: Conversion of Positive SoC Margins by Removing LUM-Guided Shaves

	Efficacy Population (N = 357)
Patients having positive margins after SoC BCS, n (%)	62 (17.4%) 95% CI:13.6%, 21.7%
Secondary endpoint: Percent of patients converted from positive margins after SoC BCS to final negative margins by excising LUM-guided shaves, n (%)	14.5% (9/62) 95% CI: 6.9%, 25.8%

BCS: Breast conserving surgery; CI: Confidence interval; SoC: Standard of care

2.5.2.2 Average Volume of LUM-Guided Shaves and Contribution to Total Excision Volume and Impact to Perceived Patients' Cosmesis

Table 15 in Section 7.1.8.2 summarizes the results for tissue volumes from the SoC BCS and LUM-guided shaves and contribution to total tissue volume. Overall (N = 357 patients), results show the contribution of LUM-guided shaves to the total volume of resection was approximately 10 cm^3, or 9.4% (± 14.1%), with an average number of LUM-guided shaves removed of 1.0 ± 1.4. When at least 1 LUM-guided shave was removed (N = 166 patients), the mean contribution of LUM-guided shaves to the total volume was 20.3% (± 14.5%), with

an average of LUM-guided shaves removed of 2.2 ± 1.4. As described below (Section 2.5.3), an exploratory endpoint result suggests that the amount of additional tissue removed when using the LUM System does not negatively impact patient's perceived cosmesis 3 and 6 months after the surgery.

2.5.2.3 Patient-Level Sensitivity and Specificity Analyses

The sensitivity and specificity results presented in Section 2.5.1 (and in more detail in Section 7.1.7.2) address the diagnostic performance of the LUM System at the tissue level, as each patient produced readings for each cavity orientation. However, Lumicell also investigated extrapolating tissue-level results to patient-level results with 2 different approaches (described in Table 16).

Approach 1 captures all patients that benefited from having residual cancer removed that was left behind during the SoC procedure, resulting in a per-patient sensitivity of 54% (95% CI: 40%, 68%) (Table 17). That is, 54% of the patients with residual cancer after the SoC BCS had at least some residual cancer removal facilitated by the LUM System. However, under the narrow definition used in Approach 2, 5 patients were reclassified from true positives to false negatives because at least some cancer was missed by the LUM System, resulting in a patient-level sensitivity of 44% (95% CI: 30%, 59%).

It is important to note that the proposed indication for use for the LUM System is as an adjunct to SoC BCS and is not intended to replace any of the SoC procedures. As such, the false negative patients still undergo all the necessary SoC procedures, including second surgeries when needed.

The patient-level specificity was 58% (95% CI: 52%, 63%) and applied to both approaches (same definitions for both). However, as described below, false positive tissue removal did not appear to impact patient perception of cosmesis. Moreover, 9 of these patients benefited by having their positive margins converted to final negative margins by excising this LUM-guided shave.

2.5.3 Exploratory Endpoint: Patient Reported Outcomes Measures and Impact to Cosmesis

To investigate if the additional tissue removed guided by the LUM System had an impact on patient's perceived cosmesis, a PROM survey was implemented as an exploratory endpoint (Section 7.1.9). The primary aim of the survey was to collect data from patients in the treatment arm that had no LUM-guided shaves removed and those who had at least 1 LUM-guided shave removed. Although there was an average of 20% increase in total tissue removal in the group with at least 1 LUM-guided shave removed compared to the group with no Lumicell shaves removed, the survey data demonstrated that the patient's perspective on their own breast satisfaction did not change when LUM-guided shaves were removed, indicating that there was no negative impact to cosmesis.

2.5.4 Efficacy Conclusions

For Pivotal Study CL0007, the efficacy results demonstrated success in detecting residual cancer and guiding the removal of the cancerous tissue that would have otherwise remained undetected after completing their SoC BCS in 27 patients (7.6%; 27 out of 357 patients; 95.0% CI: 5.0%, 10.8%; Section 7.1.7.1), thereby surpassing the co-primary endpoint's performance goal of 3%. Residual cancer removed in LUM-guided shaves included Grade 3 histology in 13 of 27 patients, and residual cancer ≥ 1 mm in size in 18 of 27 patients (Table 11).

The diagnostic performance of the LUM System also successfully met the specificity endpoint and exceeded the preset performance goal of 60% by 24.5 percentage points, though it failed to also meet the sensitivity endpoint of 40% by 3.6 percentage points. However, the LUM System performance clearly provided non-random information to surgeons to either take or not take an additional shave, with a resulting Youden Index of 0.36 and an ROC AUC of 0.7. These results demonstrate that the predictive ability of the system is better than randomly taking selected shaves.

In addition, the use of the LUM System led to the following clinically meaningful results:

- Approximately 15% (9) of patients with pathology-positive margins after SoC BCS resulted in pathology-negative margins after additional LUM-guided shaves (Section 7.1.8.1)
- 22 out of 357 (6.2%) patients had residual cancer removed in LUM-guided shaves from lumpectomy cavity orientations with negative margins after the SoC BCS. Out of these 22, 19 had all negative margins after SoC BCS. That is, these 19 patients would have completed their initial SoC procedure with cancer remaining in the lumpectomy cavity and likely would have not received a follow-up surgery because the SoC margins were negative (Section 7.1.7.1).
- Across the efficacy population, LUM-guided shaves contributed to approximately 9% of the total tissue removed, with an average of 1 shave removed per patient. For those with at least 1 LUM-guided shave removed, the tissue accounted for approximately 20% of the total tissue removed, with an average of 2 shaves removed per patient (Section 7.1.8.2).
- The exploratory endpoint of patient satisfaction suggests that removal of LUM-guided shaves did not have significant impact on patient's perceived cosmesis, although the study was not powered for this endpoint (Section 7.1.9).

In summary, the LUM System provided breast cancer surgeons with a novel, adjunctive, *in vivo* imaging capability to detect and guide the removal of residual cancer otherwise left behind during the initial SoC BCS. The LUM System is an interventional tool with demonstrable clinical benefits that improves the current SoC.

2.6 Safety Findings

The safety profile of the LUM System was characterized by 726 patients dosed at 1 mg/kg (703 breast cancer patients and 23 patients with other cancers). Chromaturia (urine discoloration) was the most frequently reported adverse event (AE), observed in 85% of patients in the safety population. This AE was expected because of the blue color of LUMISIGHT. Overall, 176 of 726 patients (24%) reported an AE other than chromaturia.

There were no deaths reported in any of the clinical studies where LUMISIGHT was administered. Life-threatening AEs (2 [0.3%] patients), serious adverse events (SAEs; 7 [1%] patients), and AEs leading to discontinuation (8 [1%] patients) were reported infrequently in the overall safety population (N = 726; Table 3).

Table 3: Overview of Adverse Events in Safety Population Dosed at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
Total AEs	633 (87%)
Chromaturia	615 (85%)
Related chromaturia	613 (84%)
AEs other than chromaturia	176 (24%)
Related AEs other than chromaturia	30 (4%)
Life-threatening AEs	2 (0.3%)
Related life-threatening AEs	1 (0.1%)
SAEs	7 (1%)
Related SAEs	4 (0.6%)
AEs leading to discontinuation	8 (1%)
Deaths	0

AE: Adverse event; SAE: Serious adverse event

Across all Lumicell clinical studies in patients dosed at 1 mg/kg, 4 out of 726 (0.6%) patients reported an SAE related to the LUMISIGHT injection: 1 severe hypersensitivity and 3 anaphylactic reactions (Section 8.5).

Administration of LUMISIGHT is performed at the pre-operative area under medical supervision by personnel who are already trained to identify and treat hypersensitivity reactions. Therefore, each SAE was managed immediately with standard medical interventions. Three of the 4 patients recovered within 1 hour of symptom onset and had their lumpectomy either the same day or the next. One patient required admittance to the intensive care unit, fully recovered the following day, and had her lumpectomy rescheduled within 17 days.

An independent panel, consisting of 3 expert allergists and immunologists from Massachusetts General Hospital and Brigham and Women's Hospital (all instructors of medicine at Harvard Medical School), reviewed these serious allergic reactions and disagreed with 1 of the assignments as an allergic reaction. Rather, the panel classified this

case as a vasovagal reaction. The panel agreed with the severity of 2 of the remaining 3 serious allergic reactions. The fourth evaluated anaphylaxis event was considered a moderate allergic reaction by the expert panel (Section 8.5.2 and Table 26).

To mitigate risks of adverse reactions, the Sponsor has proposed to include the following warnings on the proposed label:

- Clearly indicate the risk of "life-threatening anaphylaxis" in the Highlights section and the Warnings and Precautions section.
- Advise healthcare providers that before LUMISIGHT administration, obtain history of allergy, hypersensitivity, or prior hypersensitivity reactions.
- Indicate that patients with history of multiple food or drug allergies, or other hypersensitivities, may be at an increased risk.
- Specify to always administer LUMISIGHT in a healthcare setting and have emergency resuscitation equipment and trained personnel available.
- Instruct that if hypersensitivity reaction is suspected, interrupt injection.
- Monitor patients for 15 minutes after injection.

Overall, LUMISIGHT was well tolerated, and the risk of hypersensitivity is manageable in the pre-operative hospital setting where LUMISIGHT is administered.

2.7 Benefit-Risk Summary

The LUMISIGHT and the Lumicell DVS combination product has a positive benefit-risk profile. This imaging system, as an adjunct to SoC BCS, identified residual cancer that was left behind during the SoC BCS procedure, as well as converted patients from positive margins to final negative margins by excising LUM-guided shaves. All of this was achieved by removing tissue that did not appear to impact patient's perceived cosmetic outcomes. These benefits outweigh the manageable risk of potential hypersensitivity AEs in the pre-operative hospital setting.

The LUM System enabled real-time assessment of the breast cancer lumpectomy cavity and facilitated removal of residual cancer left behind after SoC BCS. In Pivotal Study CL0007, the LUM System as an adjunct to SoC provided multiple benefits, including:

- Providing imaging results immediately available to the surgeon, requiring approximately 1 minute to scan the entire lumpectomy cavity, with all interventions adding less than 7 minutes to the operative procedure.
- Identifying residual cancer within 2-5 mm from the surface of the lumpectomy cavity, rather than on the surface of the excised lumpectomy specimen like standard margin assessment, frozen section, and other available tools. This avoids the inherent problem of specimen-based approaches, correlating the location of tumor on an excised deformable specimen surface with the location of residual tumor in the breast cavity.

- Allowing for repeat imaging of areas of concern during the initial SoC BCS to verify the removal of all positive signal areas.
- Guiding the removal of residual cancer remaining after SoC BCS in 27 of 357 (8%) patients. The residual cancer deposits excised included areas of low- and high-grade tumor ranging from 1 to 13 mm in size. Whether or not this residual disease that otherwise would have remained behind could account for recurrences following breast conserving surgery warrants further investigation.
- Converting 9 of 62 (14.5%) patients with SoC positive margins to final negative margins by excising LUM-guided shaves. In 8 of these 9 patients, a second surgery was avoided, reducing the patient and hospital burden of an additional surgery.

As for the risks of LUMISIGHT administration:

- Favorable safety profile and well-tolerated, with low frequency of non-chromaturia AEs and related SAEs (0.6% [4/726 patients]), and no device related AEs reported across the clinical study program.
- All related hypersensitivity events occurred in the pre-operative hospital setting and were managed by pre-op personnel well-trained in the identification and treatment of such allergic reactions.
- All patients fully recovered and proceeded on to SoC lumpectomy.
- To further mitigate risk of adverse reactions or device events, the Sponsor has proposed additional warnings and details in the Prescribing Information for LUMISIGHT, as listed in Section 2.6.

Considering the benefits and risks identified in the Pivotal Study, the totality of the clinical benefits of the LUM System outweigh the potential safety risks, which can be well-managed in a pre-operative hospital setting and are clearly identified in the Prescribing Information.

Given the low complication rate, minimal added operative time and, most importantly, the discovery of additional cancer left behind after a lumpectomy, the LUM System has the potential to be a critical adjunct to enhance standard practice for breast cancer patients. Hence, the benefit-risk assessment supports the proposed indication 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.

3 BACKGROUND ON BREAST CANCER

Summary

- Approximately 300,000 women were diagnosed with breast cancer in the US in 2023, with an additional 43,700 deaths.[1,2]
- Surgery is the most common treatment.
  - More than 60% of patients with early-stage breast cancer undergo BCS.[6]
  - Approximately 10-36% have a follow-up surgery due to the suspicion of residual cancer left after the initial BCS.[7,13,14]
- Current SoCs do not identify the extent of tumor accurately enough, making it challenging to achieve complete tumor excision during BCS.
- Inadequate assessment of the surgical cavity during lumpectomy procedure, further exacerbated by the inherent limitations of pathology margin assessment often leads to the need for follow-up surgeries, wide-spread use of adjuvant therapies (and their associated comorbidities), and in some cases local cancer recurrence.
- A significant unmet need remains for real-time intracavity detection of residual cancer to achieve a more complete tumor resection during the initial surgery.

3.1 Overview of Breast Cancer

Breast cancer is both a life-threatening and irreversibly debilitating disease and remains the most common cancer in women. Approximately 300,000 women were newly diagnosed breast cancer in the US in 2023, with an additional 43,700 deaths.[1,2] Over their lifetime, 1 in 8 women will be diagnosed with breast cancer.[1]

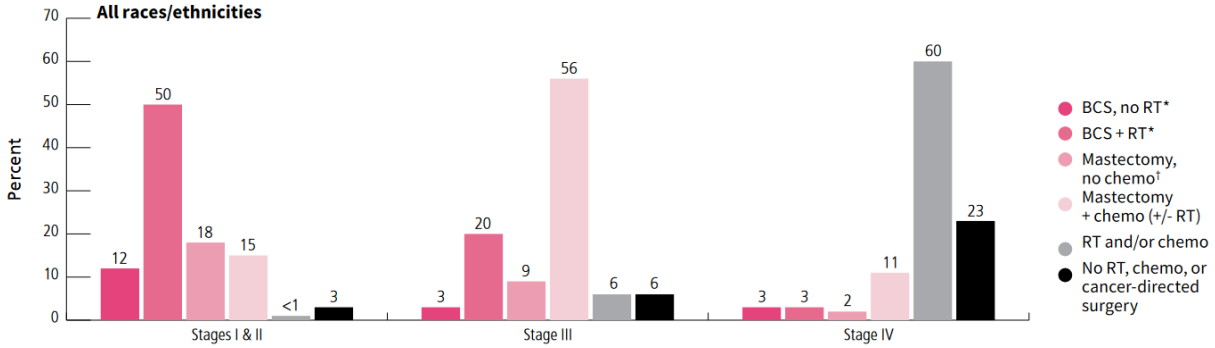
The most common type of breast cancer is invasive ductal carcinoma (IDC), which is a neoplastic proliferation of ductal epithelial cells into the breast stroma. The precursor to invasive breast cancer is DCIS, where this proliferation is separated from the breast stroma by an intact layer of basement membrane and myoepithelial cells. Cancer that begins in the lobes or lobules is called lobular carcinoma and is more often found in both breasts, which results in more frequent upstaging because growth patterns are more challenging to detect on imaging compared to other types of breast cancer.

3.2 Current Standard of Care Treatment Options and Outcomes

For most patients diagnosed with early-stage breast cancer, their primary treatment is surgery: either a mastectomy (removal of the entire breast) or a lumpectomy, also termed BCS. The goal of a lumpectomy is to remove as much cancer as possible while sparing normal breast tissue to improve cosmetic outcomes. Studies show that a lumpectomy followed by radiation therapy provides the same survival benefit as mastectomy for most women with breast cancer.[21] More than 60% of all patients (or about 200,000) with early-stage breast cancer undergo BCS as part of their treatment (Figure 3). Lumpectomy

with negative margins followed by radiation and systemic therapy provides good local control, however some breast cancer patients, including those with negative margins, still develop local recurrences, often near the site of the primary tumor.[3] Although some studies show radiotherapy reduces 10-year recurrence to approximately 2–3%,[8,9,28] a meta-analysis showed that radiotherapy reduced the 10-year risk of any first recurrence from 35% to 19.3% and the 15-year risk of breast cancer death from 25.2% to 21.4%.[29] Further studies demonstrate that incomplete tumor resection, as represented by positive margins, doubles the risk of recurrence, ultimately leading to 1 excess death for every 4 breast cancer local recurrences.[11,12]

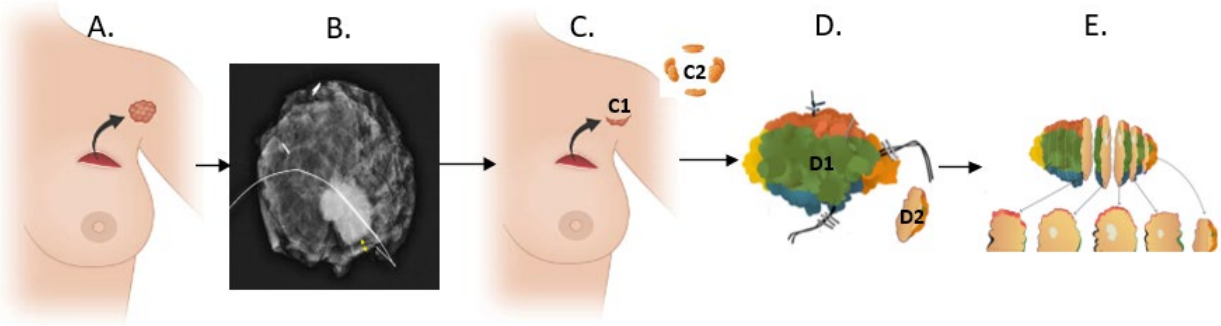
Figure 3: Female Breast Cancer Treatment Patterns (%), by Stage, 2018



BCS: Breast-conserving surgery; RT: Radiotherapy
Source: Breast Cancer Facts and Figures[30]

A SoC lumpectomy procedure is shown in Figure 4. Surgeons attempt to remove the primary cancer with a rim of normal tissue, together called the main specimen or lumpectomy specimen. Once removed, the specimen is either marked with stitches or inked by the surgeon to mark the orientations relative to the lumpectomy cavity. The surgeon may use different techniques, such as intraoperative X-ray imaging of the main specimen, to determine that the previously placed markers during the diagnostic biopsy have been removed in the lumpectomy. The surgeon may also palpate the lumpectomy cavity and do a visual inspection for grossly appearing abnormal tissue. Following visualization of the resected specimen and examination of the cavity, many surgeons remove selective cavity shave margins from the cavity deemed to be most likely to contain residual cancer, or comprehensive shave margins from all orientations. Once the surgery is completed, the main specimen and any cavity shaves are sent to pathology and oriented, sectioned, and processed for staging and margin assessment. The overall procedure consisting of the excision of the lumpectomy, together with any shave margins, is considered a SoC lumpectomy procedure.

Figure 4: Standard of Care Lumpectomy Procedure



(A) The tumor is localized and excised with a surrounding margin of healthy tissue.[31] (B) Intraoperative radiographs are taken of the lumpectomy specimen to identify if the tumor is involved in the resection margin.[32] (C) Following visualization of the tumor and determination of how close it approaches the specimen margin, selective shave margins (C1)[31] or comprehensive shave margins (C2)[33] may be performed. (D) The excised lumpectomy specimen is oriented with stiches or ink (D1)[34] and, along with the additional shaves (D2),[34] are sent to pathology for routine sectioning and assessment (E).[34]

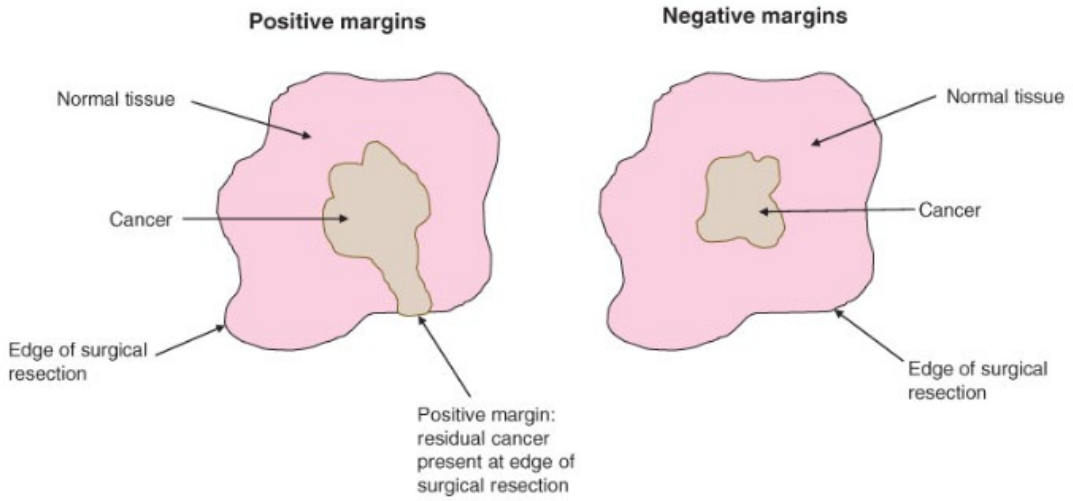
In many cases during the lumpectomy procedure, the surgeon will also make an incision in the axilla to remove the sentinel lymph nodes (SLN) for further staging. If cancer cells are found in the SLN, which may indicate metastases, the patient will receive different adjuvant treatments than if no cancer cells are found in the SLN.

With advances in diagnostic imaging and pathology techniques, more recent clinical trials have aimed to identify appropriate breast cancer patients for whom radiotherapy may be safely omitted following BCS while maintaining sufficiently low rates of local recurrence.[35,36] Local recurrence rates for DCIS have consistently been higher than those seen for Stage I breast cancers following BCS,[37] even in the setting of adjuvant radiotherapy.

3.3 Breast Conserving Surgery Limitations and Unmet Need

The effectiveness of BCS relies on excising the entire tumor at the time of lumpectomy. However, the completeness of tumor excision is difficult to ascertain at the time of surgery, and the extent of potential residual disease is determined at final pathology a week or more after the initial surgery where disease may be found present at the edges of the lumpectomy, resulting in a positive margin. For invasive carcinoma and DCIS, a positive margin is defined as having tumor present at the inked side of the outermost surface of the lumpectomy specimen (Figure 5).[10,27] For DCIS, if the tumor margins are less than 2 mm but not on ink, a second surgery may be recommended.[10] If positive margins are identified by pathology, which occur in 10-36% of the patients,[13,14] a follow-up surgical procedure is typically required to re-excise additional breast tissue at that site to ensure that all gross tumor is removed. These follow-up surgeries result in significant burden to the patient and the healthcare system and create delays in post-surgery treatment.

Figure 5: Margin Assessment of Lumpectomy Specimen



Schematic of margin assessment of lumpectomy specimen, comparing positive (left panel) to negative (right panel) margins. Identification of positive margins on the lumpectomy specimen will commonly result in additional surgery.[15]

Oncoplastic breast surgery (OBS) for BCS is an emerging field, due to the positive impact on cosmesis.[38,39] The goal of OBS is to achieve better cosmetic outcomes by rearranging the breast tissue after the main specimen has been removed. However, when positive margins occur, there is a higher incidence of mastectomy after OBS than in BCS because during OBS the breast tissue is rearranged, making it difficult to localize the initial specimen orientation after tissue reshaping.[40]

Current perioperative techniques approved by the FDA to identify residual tumor or positive margins in breast cancer all rely on *ex vivo* specimen analysis and technologies such as radiofrequency spectroscopy (Margin Probe),[17] intraoperative X-ray (e.g., Faxitron),[18] and optical coherence tomography (Perimeter OCT),[19] all of which attempt to predict the margin status, visualize the tumor within the excised specimen, or visualize the margin itself. None directly assesses the presence of residual cancer in the surgical cavity. There are also other intraoperative imaging technologies at various stages of development but not currently approved by the FDA for breast cancer.[41]

The limitations inherent with SoC lumpectomy intraoperative margin assessment techniques are well-known:[42]

- Excised breast specimens deform immediately after excision, causing surgeons and pathologists to lose specimen surface orientation relative to the lumpectomy cavity where tumor may remain, even when the specimen is inked.
- Handling and sectioning of specimens can expose tumor not actually at the margin but nevertheless attributed to the margin.

- Pathology margin assessment is completed approximately 1 week after the surgery, not in real-time, and results in 10-36% positive margins,[13,14] most of which require a follow-up surgery.
- Given the inherent limitations of microscopic examination, it's estimated that <1% of the surface area is microscopically examined (i.e., if a spherical shape with a 2 cm diameter is assumed for the main specimen and sections of 6 µm are sampled every 2 mm, then <1% of the surface of this sphere is presented for examination).[20]
- In 65% of lumpectomy positive margins, no tumor is found in a subsequent cavity shave from the same orientation.[13,16]
- In 19% of margins deemed negative by standard histopathology assessment, tumor is found in a subsequent cavity shave from the same orientation;[16] these are pathologically diagnosed false negative margins that leave tumor behind after standard surgery. This may be due to under-sampling of resected tissue or small satellite tumors that are not feasible to identify with current methods.

Inadequate assessment of the surgical cavity during lumpectomy procedure, further exacerbated by the inherent limitations of pathology margin assessment, limit the physician's ability to accurately predict the presence of residual disease in the patient with SoC treatment. This often leads to the need for follow-up surgeries, wide-spread use of adjuvant therapies (and their associated comorbidities), and in some cases can lead to local cancer recurrence.

Overall, there is a clear unmet need for a real-time, intracavity tool to enable surgeons to more effectively determine the extent of tumor left behind after a lumpectomy.

4 PRODUCT DESCRIPTION

Summary

- LUMISIGHT is administered 2-6 hours prior to imaging at a dose of 1 mg/kg by IV injection over 3 minutes.
- LUMISIGHT is optically inactive when intact and produces a fluorescent signal after its peptide chain is cleaved by enzymes that are at higher levels in and around tumor and tumor-associated cells than normal cells.
- After the SoC lumpectomy is completed, the surgeon inserts the Lumicell DVS probe in the lumpectomy cavity to scan for residual cancer.
  - Regions suspected to contain cancer are highlighted in red, indicating the location of additional tissue to resect.
  - Results are immediately available to the surgeon.
  - Unlike standard margin assessment, which assesses the surface of the excised lumpectomy specimen, LUM-guided surgery is a cavity-based approach that identifies residual tumor within the lumpectomy cavity.
  - LUM-guided surgery avoids the inherent problem of correlating the location of tumor on an excised deformable specimen surface with the location of residual tumor in the breast cavity.
  - LUM-guided surgery allows for repeat imaging of areas of concern during the initial operation to verify the removal of all positive signal.

4.1 Proposed Indication

The LUM System is a combination product consisting of an optical imaging agent, LUMISIGHT, and an imaging device, the Lumicell Direct Visualization System (DVS). The proposed indication is 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. The combination product is not intended to replace any procedure of the SoC lumpectomy.

4.2 Product Overview

The Lumicell DVS consists of a Workstation and a Handheld Probe (Figure 2). These components are used together to excite the optical imaging agent, LUMISIGHT, and capture and display real-time fluorescence images. The handheld probe is designed to be held comfortably in one hand, and the imaging portion fits most lumpectomy cavities (3 cm diameter).

LUMISIGHT, an activatable fluorescent imaging agent, is injected intravenously 2 to 6 hours prior to surgery and is intended to produce a fluorescence signal at sites of residual cancer.

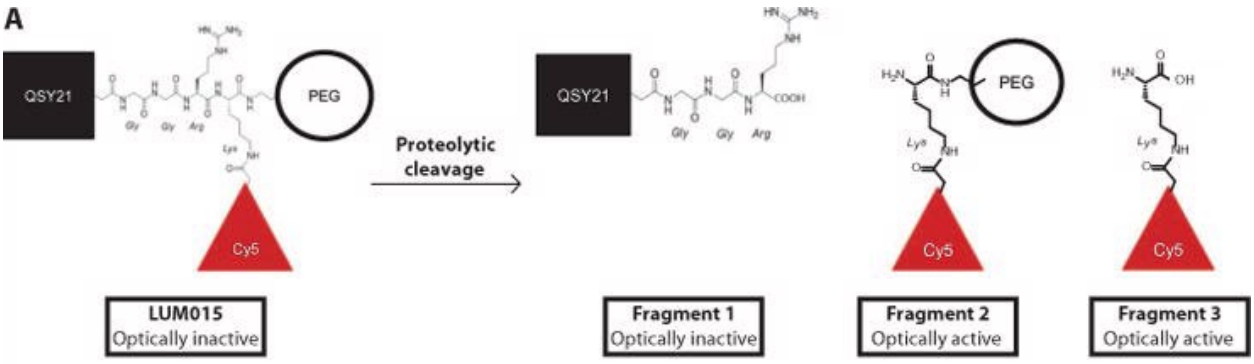
During surgery, the surgeon illuminates the cavity with a handheld probe (part of the Lumicell DVS), and the fluorescence images are analyzed by a tumor detection algorithm and displayed to the surgeon on a computer screen. Regions suspected to contain residual cancer are highlighted in the screen to assist the surgeon with where additional tissue should be removed. The goal of the combination product is to detect residual cancer left behind during the SoC BCS and guide its removal, thereby achieving a more complete cancer resection. The mechanism of action is described in detail in the following section.

The LUM System is being proposed for invasive and DCIS breast cancer. The combination product, as an adjunct to SoC BCS, was designed to fit with current operative procedures, with administration of the imaging agent (LUMISIGHT) to be performed in the pro-operative hospital setting with clinical care available from injection and through the duration of the surgery to ensure patient safety.

4.3 Mechanism of Action

The imaging agent LUMISIGHT is composed of a fluorophore, a dark quencher, an amino acid backbone, 2 spacers (Ahx and PEG2), and a ~20,000 Dalton polyethylene glycol (PEG) molecule. In LUMISIGHT's intact state (as manufactured and administered), the dark quencher absorbs any fluorescence emitted by the fluorophore, rendering the molecule fluorescently inactive. A schematic representation of LUMISIGHT activation is shown in Figure 6.

Figure 6: Schematic Representation of LUMISIGHT and Its Proteolytic Cleavage Products



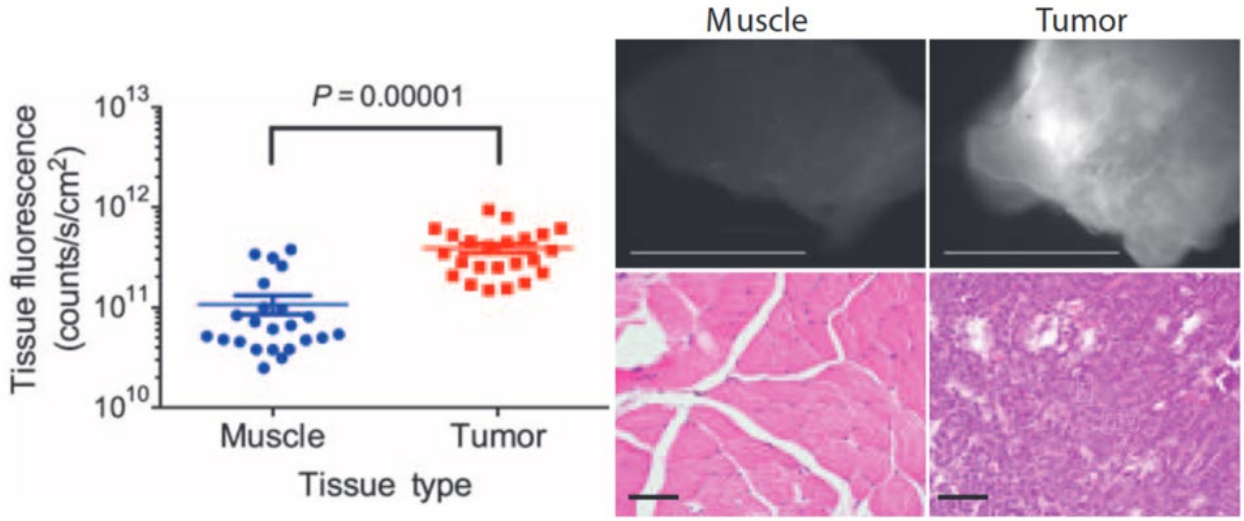
LUMISIGHT is non-fluorescent in its intact state due to the close proximity of the dark quencher (QSY21) to the fluorescent dye (Cy5) (left). Upon reaching the tumor and its surrounding area, high enzymatic activity cleaves LUMISIGHT's peptide backbone, separating the dark quencher (Fragment 1) from the rest of the molecule, generating 2 fluorescent products, Fragment 2 and Fragment 3. Figure from Whitley, et. al.[24]

LUMISIGHT is administered via a 3-minute IV injection, 2 to 6 hours prior to LUM-imaging. After cleavage, the fragment containing the fluorescence quencher (Fragment 1) separates from the rest of the molecule, leaving a fragment containing the fluorophore and PEG (Fragment 2). A smaller fluorescent fragment (Fragment 3) is also created, consisting only of the lysine amino acid conjugated to the fluorophore. This protease activation does not fully account for the increased signal in and around the tumor relative to normal tissue, and

instead is established in part by tumor-selective accumulation through the enhanced permeability and retention effect.[24] LUMISIGHT activation is more frequent in areas immediately adjacent to the tumor, reflecting a gradient of proteases present at the periphery of malignant lesions.[43] Although this property reduces the specificity of the system, it has the positive effect of helping to obtain clear margins of desirable width across the entire lumpectomy cavity. This property can be observed in representative fluorescence images from a breast cancer mouse model (Figure 7).

To produce a fluorescence signal, the design of LUMISIGHT incorporates a Cy5 dye, that when excited with a wavelength of ~630 nm it emits fluorescence with a peak emission at a wavelength of 662 nm. At these wavelengths, the light penetration depth into tissue is 2-5 mm, thus cancer within that depth from the cavity surface coproduce detectable fluorescence from activated LUMISIGHT. This wavelength and penetration depth were selected based on current practice of excising cavity shaves of approximately 5-10 mm thick, so that iterative imaging can be performed after resection of a shave without excessive tissue removal.

Figure 7: LUMISIGHT Fluorescently Labels Tumor in Pre-Clinical Mouse Model of Breast Cancer

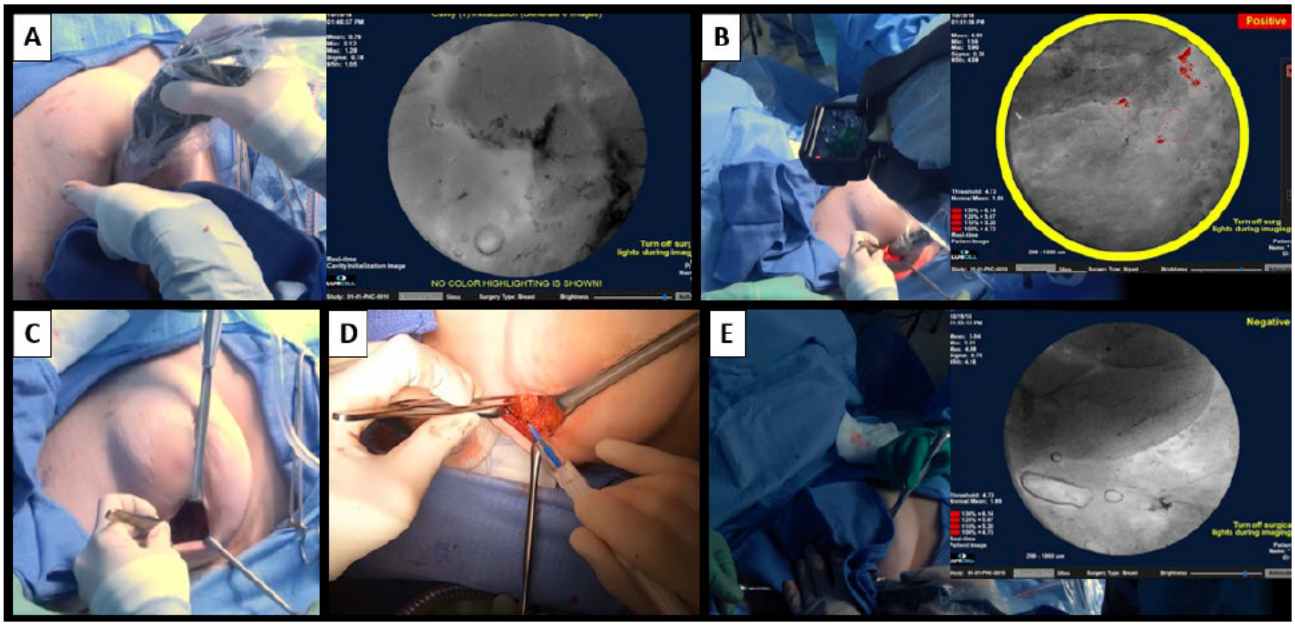


Representative LUMISIGHT fluorescence images from resected normal muscle and breast cancer are shown along with corresponding hematoxylin and eosin (H&E) histology. The gradation of LUMISIGHT activation adjacent to the tumor, sometimes referred to as a "halo", can be observed in image at the top right. Scale bars are 5 mm for fluorescence images and 500 µm for H&E images. Figure from Whitley, et al.[24]

During surgery, the handheld probe component of the Lumicell DVS is used to scan the lumpectomy cavity for activated LUMISIGHT in the tumor bed by delivering ~630 nm excitation light and measuring the fluorescence emission signal using a camera.[43–47] An imaging session starts by capturing images of bright and dark calibration standards using the handheld probe to ensure that the system is working properly. After successful system calibration, the surgeon inserts the handheld probe into the lumpectomy cavity and records 6 images from different locations to establish the patient's baseline fluorescence

(Figure 8A). From these images, the software algorithm sets an individualized fluorescence threshold for the patient above which any fluorescence signal will be considered suspicious to contain cancer. After the cutoff value is set for the patient, the surgeon may scan the lumpectomy cavity for regions with fluorescence signal above the cut off that are suspicious for containing residual cancer (Figure 8B). These regions of interest are indicated as red on the monitor and used to guide additional cavity shaves. The surgeon will then mark the location of the region with high fluorescence signal using their finger or surgical instruments before removing the probe from the cavity (Figure 8C), take a cavity shave from that location (Figure 8D), and then place the probe back into the lumpectomy cavity to confirm that the positive signal has been excised from that location (Figure 8E).

Figure 8: Use of LUMISIGHT and the Lumicell DVS to Locate Suspected Residual Cancer in the Lumpectomy Cavity



The software algorithm used to set the fluorescence cutoff value was developed using regression analyses of data collected during the CL0006 Phase C Feasibility Study in breast cancer patients. These analyses estimated the relationship between the signal above the cutoff (i.e., a LUM-positive signal) and cancer identified by pathology after SoC BCS ($p = 0.012$). The area under the ROC curve was determined to be 0.7, demonstrating that the system provides information that is not random in nature (AUC of 0.5 indicates results provide no discrimination ability, that is, the predictive ability of the test is no better than random guessing).

The LUM-guided surgery approach for breast cancer margin assessment addresses the unmet needs in BCS.[43–47] Results are immediately available to the surgeon, requiring approximately 1 minute to scan the entire lumpectomy cavity, with an average added time of less than 7 minutes to the operative procedure.[43] LUM-guided surgery has the advantage

that the location of the residual cancer within 2 to 5 mm from the surface of the lumpectomy cavity is highlighted in real-time, rather than on the surface of the excised lumpectomy specimen. LUM-guided surgery also allows for repeat imaging of areas of concern during the initial operation to verify the removal of all positive signal areas.

5 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Initial safety study for LUMISIGHT conducted under an Investigational New Drug (IND) submission.
- LUMISIGHT and the Lumicell DVS are a combination product designated by the FDA to have a "device primary mode of action" and was assigned to CDRH as the lead reviewer for clinical development.
- The Lumicell DVS received Breakthrough Device designation for the breast cancer indication.
- LUMISIGHT received Fast Track and Rolling Review designations for the breast cancer indication.
- An NDA for LUMISIGHT and a PMA for the Lumicell DVS have been submitted to the FDA for market approval.
- The design of and endpoints for Pivotal Study CL0007 were agreed upon with the FDA via a series of Investigational Device Exemption (IDE) communications.

5.1 Regulatory History and Milestones

Clinical development of the LUMISIGHT and Lumicell DVS combination product started under IND 111670 to evaluate the initial safety of LUMISIGHT in a Phase 1, first-in-human study. This IND was held by an Investigator at Duke University Medical Center, Durham, North Carolina, US, and was later transferred to the Sponsor (Lumicell, Inc.). This study did not include *in vivo* imaging; all tissue was imaged *ex vivo* after resection with a prototype version of the Lumicell DVS.

As the Sponsor planned further development of the combination product to conduct *in vivo* imaging, the Office of Combination Products at the FDA determined that the combination product of LUMISIGHT and the Lumicell DVS has a "device primary mode of action" and designated the Center for Devices and Radiological Health (CDRH) as the lead center. After this designation, all the clinical development for the breast cancer indication was conducted under IDE G140195, including communications and agreements with the FDA regarding the design of Pivotal Study CL0007 and its endpoints. Table 4 summarizes the major regulatory milestones for the combination product.

Table 4: Regulatory Milestones

Milestone	Date
Initial IND 111670 approved	17 May 2012
FDA designated combination product as device primary mode of action	18 September 2013
Initial IDE G140195 approved	16 January 2015
Breakthrough Device Designation for breast cancer	28 March 2018
Fast Track Rolling Review awarded to LUMISIGHT	29 October 2020
First NDA modular submission	15 July 2021
Final NDA modular submission	17 March 2023
PMA submission filed	14 April 2023

IND: Investigational New Drug; IDE: Investigational Device Exemption; NDA: New Drug Application; PMA: Pre-market approval

5.2 Clinical Development Program in Breast Cancer

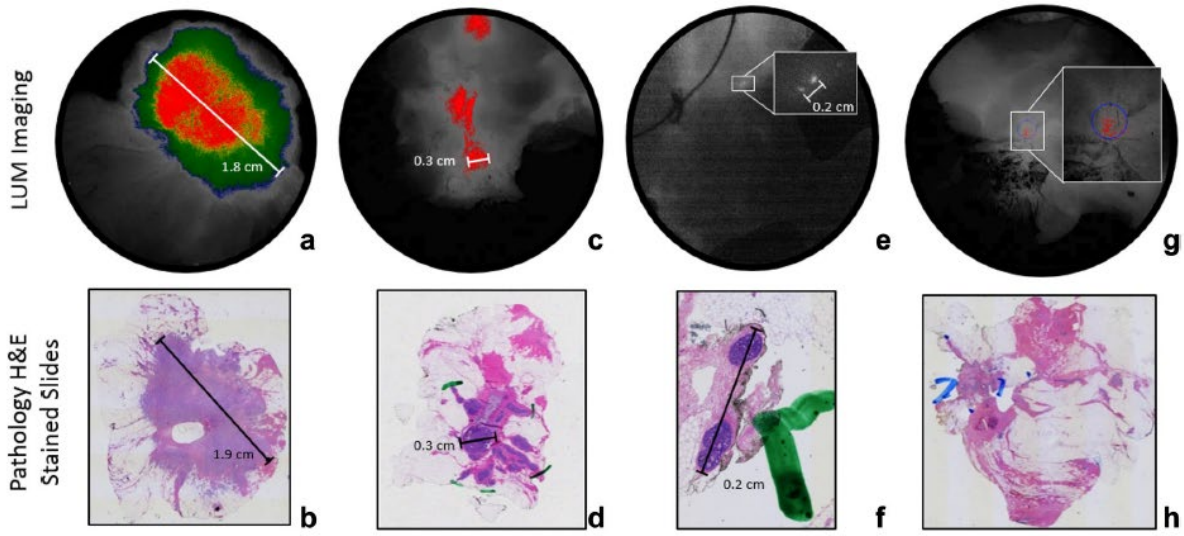
The clinical development program for the LUM System in breast cancer is comprised of 6 studies, with an additional cardiovascular safety study conducted in healthy volunteers (Table 5). Of note, several of our clinical trials, including the Pivotal Study, were funded or partially funded by grants from the National Cancer Institute (NCI), further recognizing the unmet need addressed by the LUM System.

The initial Phase 1 IDE 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 Phase 2 dose of LUMISIGHT as well as injection timepoint relative to surgery. Based on the results of this study, the recommendation was to inject LUMISIGHT approximately 6 hours prior to tumor resection at a dose of 0.5 mg/kg. Details of the study design and results were published by Whitley, et. al.[24] The dose and injection time window were further investigated in the IDE studies described below

The Phase 1 IDE Study was followed by a series of IDE feasibility studies (Phase A to Phase C) to further refine the dose for *in vivo* imaging and a reasonable imaging window:

- Phase A - Study LUM-015/2.6-001; N = 15; 5 patients were imaged without LUMISIGHT injection to measure tissue background signal, and 10 patients were injected with LUMISIGHT at doses of 0.5 mg/kg and 1 mg/kg. The purpose of this study was to re-evaluate the dose of LUMISIGHT and the development of the initial tumor detection algorithm. Lumpectomy cavities were imaged *in vivo*, as well as resected tissue was imaged *ex vivo*. Results for the dose selection are presented in Section 6.3. Examples of *ex vivo* images from cross-sections of the main specimen are included in Figure 9 showing correlation of fluorescence intensity with tumor cells. Based on the results of this study, it was determined that the optimal dose for LUMISIGHT is 1 mg/kg and the imaging windows should be 2-6 hours after injection. Details of the study design and results were published by Smith, et. al.[44]

Figure 9: Fluorescent Images from Cross-Sections of Main Lumpectomy Specimens



Fluorescent images captured from cross-sections of main lumpectomy specimens (top) show spatial correlation with tumor cells from corresponding pathology slides stained with H&E (bottom). Correlation is observed for both invasive ductal carcinoma (a,b,c,d) and DCIS (e, f, g, h). Source: Smith, et. al.[44]

- Phase B - Study LUM-015/2.6-001; N = 45 injected at 1 mg/kg. In this study, the tumor detection algorithm was further developed by implementing a patient-specific baseline to account for each patient's background fluorescence signal. No SAEs related to injection of LUMISIGHT were reported. Details of the study design and results were published by Smith, et. al.[45]
- Phase C - Study CL0006; N = 234 injected at 1 mg/kg. This multicenter study focused on training surgeons to use the combination product and to refine and finalize the Sponsor's cancer detection algorithm. With the larger population of patients, the tumor detection algorithm was finalized, implemented, and locked in for use in the Pivotal Study. The first serious and most severe AE (life-threatening) of anaphylaxis was observed in this study, leading to revisions to the exclusion criterion for patients with history of allergic reactions to contrast agents. Details of the study design and results were published by Hwang, et. al.[46]

The Pivotal Study CL0007 was a prospective, multisite study (N = 406) to determine the safety and efficacy of the contrast agent LUMISIGHT and the Lumicell DVS, both as an adjunct procedure to the SoC BCS to identify residual cancer remaining in the patients.[47]

A cardiovascular safety study (CLP00201) in healthy volunteers (N = 32) was also completed to further evaluate safety, with results demonstrating no impact to cardiac repolarization from LUMISIGHT.

Also, a feasibility study (CLP0008) in breast cancer patients undergoing neoadjuvant therapy (a population excluded from the previous breast cancer studies) added 12 patients to the safety analysis population. Results from this study are not available at the time of preparation of this briefing document.

A summary of each of the clinical studies conducted for the NDA submission is provided in Table 5. All clinical studies were designed and conducted according to the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Harmonised Guideline, Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), and according to the Declaration of Helsinki that was in place during the time the study was conducted.

Table 5: Clinical Development Studies Completed in Breast Cancer and Cardiovascular Safety Study in Healthy Volunteers

Study ID	Phase, Design	Indication	Study Objectives	Patients Injected with LUMISIGHT
DUK1-12-137	**IND** Phase 1 Single site, nonrandomized, open-label, uncontrolled study	Breast cancer, sarcoma	Primary Determine a safe and recommended Phase 2 dose of LUMISIGHT Secondary Obtain imaging information of the tumor and any adjacent normal appearing tissue; obtain PK/PD of LUMISIGHT; and analyze cathepsin protease expression in tumors	15 (3 breast, 12 sarcoma) (6 at 0.5 mg/kg; 6 at 1 mg/kg; 3 at 1.5 mg/kg)
CLP00201	**IND** Cardiovascular safety study Single center, randomized, double-blind, placebo controlled, single ascending dose	Healthy volunteers	Primary Evaluate the effects of therapeutic and supratherapeutic doses of LUMISIGHT as compared to placebo on cardiac repolarization in healthy adult patients Secondary Assess the effects of therapeutic and supratherapeutic doses of LUMISIGHT as compared to placebo on HR, PR interval, QRS duration, and T-wave morphology; evaluate the safety and tolerability of therapeutic and supratherapeutic doses of LUMISIGHT as compared to placebo; and assess the PK of LUMISIGHT and Fragment 3 following administration of therapeutic and supratherapeutic doses of LUMISIGHT	24 (32 patients enrolled, 8 in the placebo-controlled arm)
LUM-015/2.6-001	**IDE** Feasibility Phase A Single site, nonrandomized, open-label, uncontrolled study	Breast cancer	Determine the dose to be used in the pivotal trial; evaluate the detection algorithm for identifying residual cancer in the tumor bed; and gather additional safety data of the Lumicell DVS in breast cancer patients	10 (5 at 0.5 mg/kg; 5 at 1 mg/kg)
LUM-015/2.6-001	**IDE** Feasibility Phase B	Breast cancer	Determine the dose to be used in the pivotal trial; evaluate the detection algorithm for identifying	45 (all at 1 mg/kg)

Study ID	Phase, Design	Indication	Study Objectives	Patients Injected with LUMISIGHT
	Single site, nonrandomized, open-label, uncontrolled study		residual cancer in the tumor bed; and to gather additional safety data of the Lumicell DVS in breast cancer patients	
CL0006	**IDE** Feasibility Phase C Multisite, open label, single arm, nonrandomized uncontrolled study	Breast cancer	Refine and verify the tumor detection algorithm; provide hands-on training for the surgeons and clinical staff that will be participating in the pivotal study; identify and address any site-specific or user specific issues; and collect safety and efficacy data	234 (all at 1 mg/kg)
CLP00008	**IDE** Feasibility Study Feasibility Multicenter, 2-arm, randomized study	Breast cancer	Develop and validate tumor detection algorithms in breast cancer patients receiving neoadjuvant therapy; and collect safety data on the use of LUM Imaging System	12 (all at 1 mg/kg)
CL0007	**IDE** Pivotal Multicenter, 2-arm, randomized, blinded study	Breast cancer	Ratio of patients with residual cancer found in at least 1 LUM-guided shave and sensitivity and specificity on a per-tissue basis of Lumicell DVS	406 (all at 1 mg/kg)

DVS: Direct Visualization System; HR: Heart rate; IND: Investigational New Drug; IDE: Investigational Device Exemption; PD: Pharmacodynamics; PK: Pharmacokinetics

6 CLINICAL PHARMACOLOGY

Summary

- LUMISIGHT's pharmacokinetics (PK) were evaluated in 2 studies showing a mean half-life value of 5.42 hours, with 5.0% and 2.0% remaining after 22 and 48 hours from injection, respectively.
- LUMISIGHT has no known pharmacodynamic (PD) effect because it is an optical imaging agent not designed to have pharmacologic effect.
- No drug-drug interactions (DDIs) have been reported for LUMISIGHT.
    - Given its lack of PD effect and lack of propensity to alter the metabolism of other drugs, clinically important changes in the PD of other drugs are not expected if co-administered with LUMISIGHT.

6.1 Pharmacokinetics

Though no specific biopharmaceutical studies of LUMISIGHT were conducted, 2 Phase 1 studies assessed the PK of LUMISIGHT and metabolites: 1 study (Study DUK-12-137) in patients with a diagnosis of soft tissue sarcoma or breast cancer for whom surgical resection was clinically indicated;[24] and a further study (Study CLP00201) in healthy patients to characterize the risk of QT interval prolongation.

In both studies LUMISIGHT was supplied as a sterile lyophilized powder for reconstitution and single-dose administration by IV injection.

6.1.1 Pharmacokinetic Evaluation

In Study DUK-12-137 with sarcoma and breast cancer patients, the PK data supports rapid clearance of LUMISIGHT. After 22 and 48 hours, only 5.0% and 2.0% of the parent drug remain in plasma, respectively. The PK data supported a multi-phased profile with linear PK. The imaging agent, LUMISIGHT, was observed to be well tolerated by study patients.

In Study CLP00201 with healthy volunteers, following a single IV administration of LUMISIGHT, the maximum plasma concentrations of LUMISIGHT were generally reached within 1 hour and plasma profiles were characterized by a monophasic decline observed for all doses (0.5-4.0 mg/kg). Mean apparent terminal half-life was similar when increasing doses between 0.5 mg/kg and 4.0 mg/kg (4.17-4.84 hours).

Results of study CLP00201 showed that LUMISIGHT was safe and well tolerated at doses up to 4.0 mg/kg administered through slow IV bolus over 3 minutes.

6.1.2 Distribution

LUMISIGHT and Fragment 3 are both distributed in a manner consistent with a 1-compartment PK model. Geometric mean LUMISIGHT distribution volume values of 44.4-49.3 mL/kg in patients with cancer and healthy patients, respectively, suggest a

distribution volume of approximately 3-3.5 L in a 70 kg individual, consistent with the plasma compartment volume.

Although the distribution volumes of Fragments 2 and 3 have not been determined pharmacokinetically in humans, direct measurement of both metabolites in tumor and non-tumor control tissues was made in patients participating in the Phase 1 study. Significant distribution of LUMISIGHT, Fragment 2 and Fragment 3 into tumor tissues in all patients was observed, and the sum of these 3 compounds in tumor was correlated with the amount of fluorescence observed.[24] In addition, tumor fluorescence was significantly higher than matched normal tissue fluorescence, indicating preferential distribution of fluorescent fragments in tumor.

6.1.3 Clearance, Metabolism, and Elimination

In vitro studies indicated that LUMISIGHT is metabolized primarily by cathepsin protease enzymes, but not by cryopreserved human hepatocytes or recombinant human CYP enzymes. LUMISIGHT was designed to be metabolized *in vivo* via proteolysis at Lys-Arg bonds present in the peptide backbone, resulting in the release of fluorescent Fragments 2 and 3 that serve as optical imaging agents. LUMISIGHT is structurally distinct from typical small and large molecule therapeutic drugs and appears to undergo no to minimal hepatic metabolism.

Elimination of LUMISIGHT from the systemic circulation was fairly rapid at all dose levels studied in all human patients. Using the longest LUMISIGHT mean half-life value of 5.42 hours in patients with cancer, approximately 95% of the dose would be eliminated within 24 hours after dosing.

Although the routes of elimination for LUMISIGHT have not been studied in humans, a major pathway is thought to be renal excretion of LUMISIGHT and metabolites as dark blue/green colored urine, reflecting the presence of the similarly colored parent drug, which has been observed in essentially all patients receiving LUMISIGHT.

The high-water solubilities of LUMISIGHT and both Fragment 2 (PEGylated-Cy5 dye) and Fragment 3 (Cy5-Lys), plus their respective molecular weights (< 25 kDa) suggest they are candidates for glomerular filtration, and passive reabsorption could be limited by the existence of negative charges on both of the sulfonate groups on the sulfo-Cy5 moiety, thus enabling urinary excretion as a route of elimination for all 3 compounds.

6.2 Pharmacodynamics

LUMISIGHT is prepared only for IV administration and thus is considered to have complete bioavailability. There is no effect of food on LUMISIGHT bioavailability due to the use of IV administration only.

LUMISIGHT has no known PD effects because it is an optical imaging agent not designed to have pharmacologic effect. In addition, development of exposure-response relationships for efficacy or safety was not possible because patients in the efficacy trials received the

optical imaging agent only at the dose level of 1 mg/kg, and because no PK blood samples were obtained in these studies.

6.2.1 Drug-Drug Interactions

LUMISIGHT as a Substrate or Inhibitor of CYP Enzymes

In vitro studies using human biomaterials indicate that LUMISIGHT is not a substrate or inhibitor of recombinant human CYP enzymes rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6, and rCYP3A4. Accordingly, clinically important DDIs perpetrated by CYP substrates on LUMISIGHT or by LUMISIGHT on CYP substrates are not expected.

Effects of CYP P450 Enzyme Inducers on LUMISIGHT

As LUMISIGHT is not significantly metabolized *in vitro* by cryopreserved human hepatocytes or recombinant human CYP enzymes and is indicated for single dose use only, clinically important changes in LUMISIGHT metabolism are not expected if it is co-administered with CYP inducers.

Effects of LUMISIGHT on the Pharmacokinetics of Other Drugs

As LUMISIGHT is not metabolized significantly *in vitro* by cryopreserved human hepatocytes and it is not metabolized by nor inhibits individual recombinant human CYP enzymes, clinically important changes in the metabolism of drugs metabolized by the customary hepatic enzymes are not expected if co-administered with LUMISIGHT.

In summary, no pharmacodynamic DDIs have been reported for LUMISIGHT.

6.3 Selection of Dose and Regimen

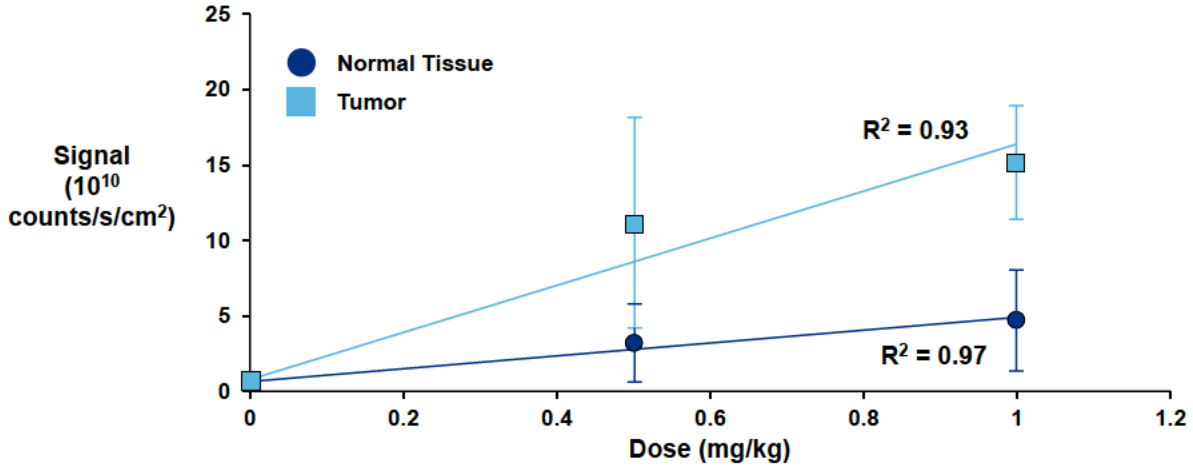
Selection of the recommended LUMISIGHT dose and time of administration relative to surgery was initially based on the results of the Phase 1 DUK1-12-137 study. However, this initial study only included 3 breast cancer patients and imaging was only performed in resected tissue. Thus, the Sponsor decided to expand the dose selection in the first breast cancer *in vivo* imaging study under the IDE Phase A study (LUM-015/2.6-001).

To accommodate pre-surgery workflows and patient management, the IDE Feasibility Phase A study expanded the time window for administration of LUMISIGHT from ~6 hours based on results of the Phase 1 study to explore a range of 2-6 hours prior to surgery. In the Phase A study, the minimum acceptable injection to imaging time window was determined by finding the shortest time point at which the tumor detection algorithm successfully predicted the presence of tumor, as confirmed by pathology. This time point occurred in a patient who was imaged 1 hour 43 minutes after injection with LUMISIGHT. However, another patient was imaged 1 hour 41 minutes after injection, and although there was no tumor found, it was believed that a 2-minute difference was not relevant. Thus, those patients with an imaging time window of less than 1 hour and 41 minutes were

excluded from the initial efficacy analysis. Based on these findings, a LUMISIGHT administration time of 2-6 prior to surgery continues to be used in further trials.

A dose-response analysis of IDE Phase A study data was conducted to identify the optimal dose for further clinical development. Resected samples from normal and tumor tissue were imaged and compared with pathology slides as presented in Figure 9. The results indicated that the fluorescence signals from tumor and normal tissue increase linearly with dose (Figure 10).

Figure 10: Fluorescence Signal Proportional to Dose



Data from breast cancer patients in Phase A suggest that signal increases linearly with dose for both tumor and normal tissue. Data points show the mean tumor and normal tissue signal at each dose (N = 3 at 0 mg/kg, N = 5 at 0.5 mg/kg and N = 4 at 1 mg/kg). Error bars indicate the standard deviation from the mean. Lines indicate a linear fit with the goodness of fit represented by R^2.

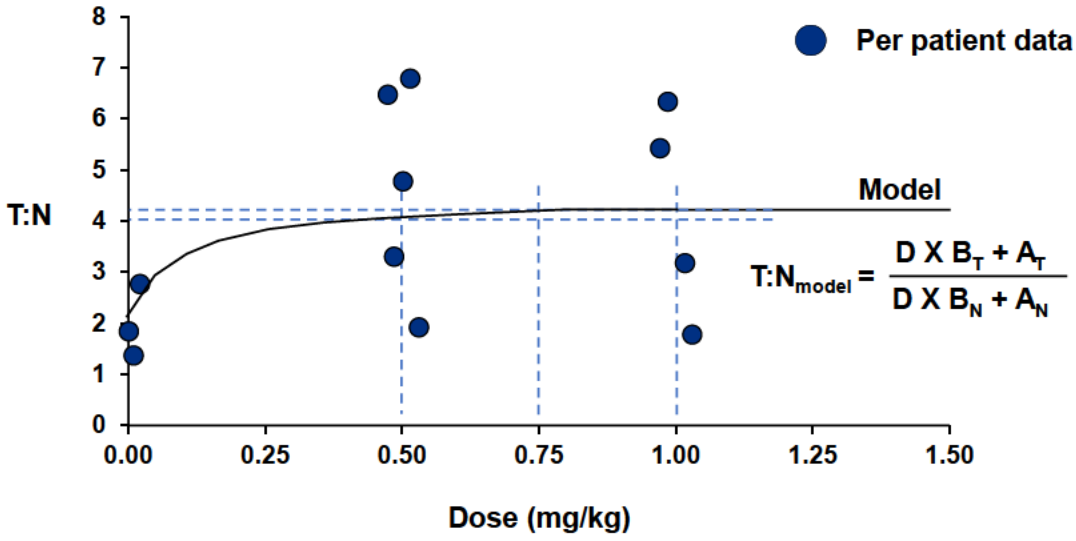
Based on the observation of linear dependency of signal with dose, it was hypothesized that at 0 mg/kg the tumor (*T*) to normal tissue (*N*) signal ratio (T:N) corresponds to the contrast from autofluorescence signals between tumor and normal tissue (~2:1). As the dose increases, the signal from tumor and normal tissue overcomes the autofluorescence signal and T:N should approach the contrast obtained by preferential biodistribution and activation of LUMISIGHT in tumor. This hypothesis was used to build a simple model to predict the behavior of T:N as a function of dose given by:

$$T{:}N_{model} = \frac{D \times B_T + A_T}{D \times B_N + A_N}$$

where D is dose (in mg/kg), B_T is tumor signal increment per unit dose, A_T is tumor background (autofluorescence) signal, B_N is normal tissue signal increment per unit dose, and A_N is normal tissue background (autofluorescence) signal (Figure 11).

The model predicts that at doses above 1 mg/kg, T:N is essentially constant, suggesting that higher doses may not improve T:N.

Figure 11: Dose-Response Model



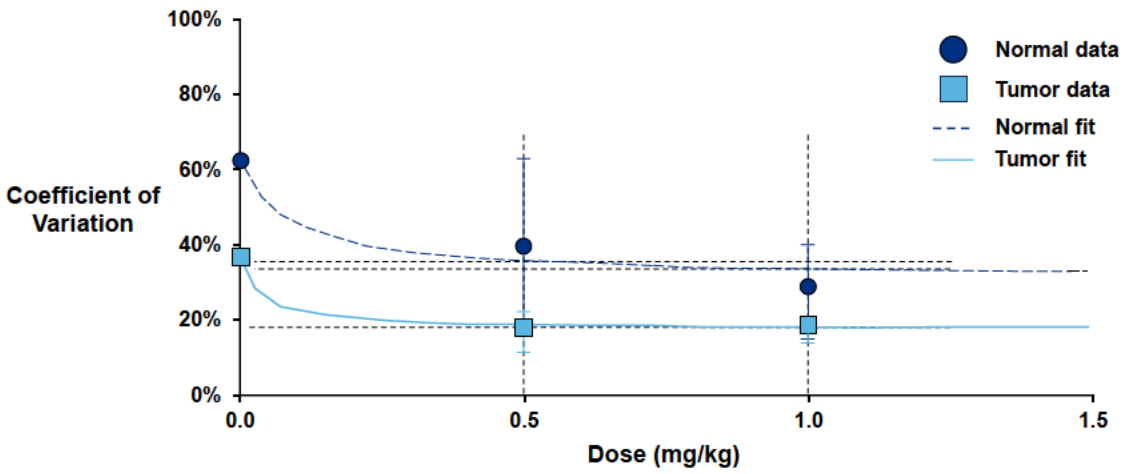
N: Normal tissue; T: Tumor
T:N data from Phase A patients (N = 11) fit Lumicell's dose-response model. Blue dotted lines plotted to note lower expected T:N at 0.5 mg/kg than at 1 mg/kg.

The data from the Feasibility Phase A study also suggested that at lower doses, the T:N coefficient of variation increases. Large variations in signal may result in overlap between tumor and normal tissue signal making it difficult to distinguish between the 2 types of tissues that can lead to false positives or false negatives. Another model was developed to predict the coefficient of variation for T:N as a function of dose, given by:

$$CV_i(D) = \frac{C_{1,i} \times D + C_{2,i}}{B_i \times D + A_i}$$

where D is dose (in mg/kg), i represents either tumor (T) or normal tissue (N), and A_i and B_i are the fitted parameters from the T:N model above. At low doses, CV_i is dominated by a constant standard deviation independent of dose (represented by $C_{2,1}$.) and the autofluorescence signal (A_i), also independent of dose. At higher doses, CV_i is dominated by the dose dependent components due to increased signal from activated LUMISIGHT in tissue, until it levels off at $C_{1,i}/B_i$. The tumor and normal tissue data were used to fit for the model parameters $C_{1,i}$ and $C_{2,i}$. The simple model prediction fits the data well in the dose and signal ranges tested, as shown in Figure 12.

Figure 12: Model Predicts Near Optimal Dose of 1 mg/kg



The coefficient of variation model fits well to the study data and shows a sharp increase in coefficient of variation below 0.5 mg/kg. Blue dotted lines are plotted to guide the reader to identify the "near optimal" dose of 1 mg/kg based upon the coefficient of variation in normal tissue.

These results show that as the dose decreases, there is a sharp increase in the coefficient of variation below 0.5 mg/kg and at higher doses, the coefficient of variation appears plateaus at around 1 mg/kg.

Based on the findings from Figure 11 and Figure 12, a dose of 1 mg/kg was selected for the breast cancer indication with an injection of LUMISIGHT 2-6 hours prior to surgery.

7 CLINICAL EFFICACY

Summary

- The safety and efficacy of LUMISIGHT in patients with breast cancer (N = 406) was evaluated in a multicenter, prospective, two-arm randomized, blinded study (CL0007).
    - Patients were randomized 10:1 to Lumicell-guided surgery (treatment group, N = 357) or not (control group, N = 35) to mitigate surgical bias (study was not powered to detect differences between treatment and control group).
- The Pivotal Study CL0007 included 3 co-primary efficacy endpoints:

Primary Endpoints	Performance goal, LL of 95% CI	Study Results
Removal of residual cancer after the SoC	> 3%	7.6% (95% CI: 5.0%, 10.8%)
Sensitivity	> 40%	49.1% (95% CI: 36.4%, 61.9%)
Specificity	> 60%	86.5% (95% CI: 84.5%, 88.3%)

CI: Confidence interval; LL: Lower limit; SoC: Standard of care

- Study CL0007 met 2 of the 3 co-primary endpoints: removal of residual disease and tissue-level specificity endpoints were met; tissue-level sensitivity endpoint was missed.
- Additionally, 14.5% (9 out of 62) of patients with positive margins after SoC BCS resulted in negative margins after excising LUM-guided shaves.
- LUMISIGHT facilitated removal of tumor left behind after standard lumpectomy surgery, most of which would have otherwise remained undetected.
- As an adjunct to SoC BCS, the LUM System combination product successfully demonstrated the removal of more cancerous tissue for a more complete resection, hence providing a superior surgical intervention leading to fewer second surgeries.
- Given that the LUM System is intended to be an adjunct to and not a replacement for any of the SoC BCS-related activities, the false negative patients still undergo all necessary SoC procedures, including second surgeries when needed.
- Patient reported outcome data suggest that cosmesis results were similar for those who had at least 1 LUM-guided shaves after SoC BCS and those who did not have LUM-guided shaves after SoC BCS.

7.1 Pivotal Study CL0007

7.1.1 Study Design

The Pivotal Study (CL0007) was a multicenter, two-arm, randomized, blinded trial with a total 406 patients injected with LUMISIGHT at 1 mg/kg. The study was designed to evaluate the safety and efficacy of LUMISIGHT and the Lumicell DVS to detect residual cancer in the cavity as an ***adjunct*** to the SoC lumpectomy procedure. Randomization was implemented to prevent surgeon bias and not for efficacy comparisons between the 2 arms. This is further described in Section 7.1.1.2. The Pivotal Study was conducted to support the market applications for LUMISIGHT and the Lumicell DVS.

The study recruited breast cancer patients from 14 medical centers throughout the US, representing a diverse geographical distribution of enrolled subjects and practice settings, including 10 academic-affiliated institutions and 4 non-academic hospitals.

A representation of the study process is illustrated in Figure 13. All consented and eligible patients in this study had breast cancer (N = 406) and were scheduled to undergo a lumpectomy procedure. The patients were injected with LUMISIGHT (1 mg/kg) 2-6 hours prior to surgery. Surgeons were asked to document their intent (location of tissue removal and reason for tissue removal) on removing SoC tissue prior to using the Lumicell DVS. If the SoC shaves were not removed according to plan, the surgeon was required to document their reason. This declaration of the intent of SoC tissue removal was required per the protocol to eliminate bias in SoC tissue removal. Once the surgeon declared that the SoC procedure was completed, the patient was then randomized at a rate of 10:1 to undergo LUM-guided imaging (***treatment arm***) or no LUM-guided imaging procedure (***control arm***). To mitigate any potential bias to the surgical procedure introduced by using the LUM System, all study personnel remained blinded to the patient's randomization arms until the surgeon completed the planned SoC BCS. For patients randomized to the treatment arm, the surgeons scanned the tumor bed to collect images of the cavity walls and excised LUM-guided shaves as indicated by the Lumicell tumor detection algorithm. No more than 2 LUM-guided shaves were allowed to be excised from a single cavity orientation. Standard of care margin assessment was performed by a pathologist on all the tissue removed during the SoC procedure, as well as any tissue removed as guided by the LUM System once the surgery is done. To avoid possible bias from the pathology review, pathologists reviewing tissue slides were blinded as to whether the specimens were SoC shave margins or LUM-guided shave margins, as described in Section 7.1.1.3.

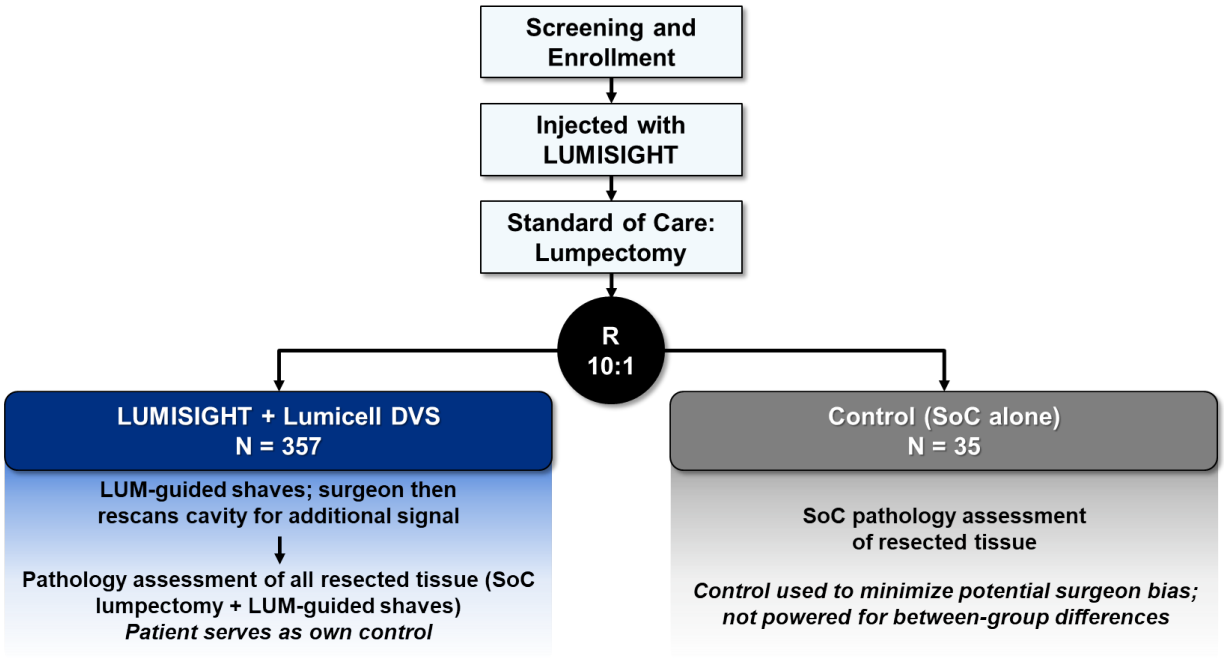
To evaluate how the use of the LUM System impacted the surgical outcome, tissue removed during both the SoC procedure and under LUM-guidance were labeled using unique study protocol specified nomenclature for naming the shave margins to correlate the tissue analysis results in the pathology report without revealing the indication for the shave (i.e., SoC or LUM-guided). This information was later entered in the CRFs to enable the imaging data analysis to be correlated with the appropriate pathology results. Thus, the surgical outcome for each of the patients in the treatment arm with and without LUM-guided

shaves can be determined during data analysis. Therefore, every patient in the treatment arm ultimately served as their own control to evaluate surgical outcomes.

LUMISIGHT injection prior to randomization increased the number of patients that contributed to the safety analysis and decreased the likelihood that blinding would be revealed prior to the completion of the SoC lumpectomy due to an injection related AE (i.e., presence of discolored urine). Patients that were randomized to the control arm and patients that were discontinued prior to randomization contributed to the primary safety endpoint but were not included in the efficacy analysis.

The Schedule of Events (SoE) for the study is provided in Appendix 12.1.

Figure 13: Study Procedure and Surgical Workflow Chart



LUMISIGHT: Study drug treatment; SoC: Standard of care

7.1.1.1 Positive Margin Definitions

Positive margins were defined using the latest consensus from the Society of Surgical Oncology as follows:

- Invasive cancer with or without associated DCIS: cancer cells present on ink[27]
- Ductal carcinoma in situ (no invasive): DCIS present within 2 mm from the inked surface[10]

7.1.1.2 Randomization

Randomization was performed at a ratio of 10:1; that is, on average, for every 10 patients undergoing LUM-guided tissue resection after SoC, 1 patient completed the SoC lumpectomy procedure alone. The randomization was intended to mitigate potential for

surgical bias by introducing uncertainty to the surgeon as to whether they would have the additional opportunity to remove more tissue than their SoC lumpectomy when further guided by the LUM System. The 10:1 ratio was selected based on prior clinical studies that supported other imaging agent efficacy trials. We note that this study was not powered to detect differences between the treatment and control arms; however, each patient in the treatment arm served as their own control with analysis based on paired data points of final margin pathology after standard lumpectomy and final margin pathology after standard lumpectomy plus additional LUM-guided cavity shaves.

This randomization ratio was discussed and agreed upon with the FDA.

7.1.1.3 Blinding

All patients were administered LUMISIGHT regardless of study arm; thus, no blinding to administration of the investigational imaging agent was required. In the operating room, after the surgeon declared the SoC lumpectomy procedure complete, the clinical coordinator connected to the electronic data capture (EDC) software and revealed the arm to which the patient was randomized utilizing the Randomization Module, which was programmed with the study specific randomization scheme. Once randomization was revealed, all parties were unblinded to the arm to which the patient was assigned (Investigator and Sponsor).

Additionally, pathologists were blinded as to whether the shave being examined was a SoC shave or a LUM-guided shave by using unique protocol specified nomenclature for naming the shaves.

7.1.1.4 Eligibility Criteria

As this study is part of the Sponsor's clinical development program to investigate the safety and efficacy of LUMISIGHT and the Lumicell DVS in female breast cancer patients, all participants enrolled were women. Males with breast cancer (~1% of breast cancer patients)[48] usually undergo mastectomy procedures and only rarely have lumpectomies,[49] and thus would not be likely to have been eligible for this study.

According to the most recent Surveillance, Epidemiology, and End Results Program Cancer statistics published by the NCI,[48] the incidence of breast cancer is essentially 0 in females under 20 years of age. Thus, given the rarity of breast cancer in the pediatric population, this study only included females aged 18 years and older. The eligibility requirement of an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 standardized the enrollment across institutions and ensured that enrolled patients had a high level of performance status prior to clinical trial enrollment.

7.1.1.4.1 Inclusion Criteria

- Patients were female, 18 years of age or older and had histologically or cytologically confirmed primary invasive breast cancer, DCIS, or primary invasive breast cancer with a DCIS component.

- Patients were required to have been scheduled for a lumpectomy procedure, able and willing to follow study procedures and instructions, and have signed an informed consent form (ICF).
- Eligible patients were required to meet minimum standards for organ and marrow functions, as well as have an ECOG Performance Status of 0 or 1.

For full details of all the inclusion criteria for the study, refer to Appendix 12.2.

7.1.1.4.2 Exclusion Criteria

- Patients with a diagnosis of bilateral breast cancer and were undergoing a bilateral resection procedure.
- Patients who were pregnant at the time of diagnosis of their breast cancer, were unwilling to use 2 medically acceptable forms of contraception if sexually active on entering the study and for 60 days after injection of LUMISIGHT.
- Patient who had received an investigational drug within 30 days of enrolment.
- Patients receiving neoadjuvant therapies were excluded from the study.
- Patients who were planned to have administration of blue dyes for sentinel lymph node mapping prior to the LUM imaging procedure were also excluded from the study.

  For sentinel lymph node resection, typically a radiotracer (Tc99) is injected into the breast prior to surgery. However, common practice is to use a second tracer in the form of blue dyes for visual identification. One limitation of the LUM System is that these blue dyes emit fluorescence signals at wavelengths that overlap with activated LUMISIGHT emission; thus, they can produce confounding fluorescence detection by the Lumicell DVS. To mitigate this challenge in the breast clinical studies, if the radiotracer Tc99 did not generate sufficient signal to find the lymph nodes, surgeons were able to inject blue dyes into the open breast cavity after the imaging procedure with the LUM System was completed. This method has been previously shown to provide successful results.[26]

For full details of all exclusion criteria, refer to Appendix 12.3.

7.1.2 Study Endpoints

The Pivotal Study CL0007 included 3 co-primary efficacy endpoints and a series of secondary endpoints (Appendix 12.4).

Prior studies have shown that local recurrences often occur close to the original tumor site with histological characteristics similar to the primary tumor, implying that local recurrences may arise from residual cancer left behind during the initial SoC lumpectomy.[3] Thus, LUMISIGHT and the Lumicell DVS are designed to identify residual cancer in the lumpectomy cavity after the SoC procedure. Further, the design of LUMISIGHT, which is activated not only by the tumor but also by tumor associated cells surrounding the primary

site, assists in removing the tumor with some additional non-tumor tissue, allowing for the conversion of positive margins to negative margins.

As the goal of lumpectomy is a complete cancer resection, removing residual cancer left behind during the SoC procedure may benefit patients in the long term. Thus, the surrogate co-primary endpoint of removal of residual cancer was selected and defined as:

- Removal of Residual Cancer: out of the total population in the treatment arm, the percent of patients who had residual cancer found in at least 1 LUM-guided shave. Residual cancer was defined as tumor confirmed by pathology assessment of a LUM-guided shave after the SoC lumpectomy is completed; that is, tumor that the SoC lumpectomy procedure failed to remove.

To achieve the performance goal above as an adjunct to the SoC lumpectomy procedure, the system must trade-off between removing as much cancer as possible while also sparing non-cancerous tissue. This trade-off is determined by the tissue-level sensitivity and specificity. These endpoints measure the ability for each of the images collected with the LUM system to correctly identify regions with or without residual cancer. Thus, 2 additional co-primary endpoints were evaluated in the Pivotal Study:

- Tissue-Level Sensitivity: percent of truth standard positives that produced a LUM-positive signal.
- Tissue-Level Specificity: percent of truth standard negatives that produced a LUM-negative signal.

In addition to the primary endpoints, a number of clinically meaningful secondary endpoints were also evaluated, including:

- Number of patients with positive margins after SoC lumpectomy who were converted to final negative margins by excision of LUM-guided shaves.
- Average volume of LUM-guided shaves and contribution to total excision volume.
- Patient-level sensitivity and specificity analyses.

The full list of all secondary endpoints is provided in Appendix 12.4.

The following exploratory endpoint was also evaluated:

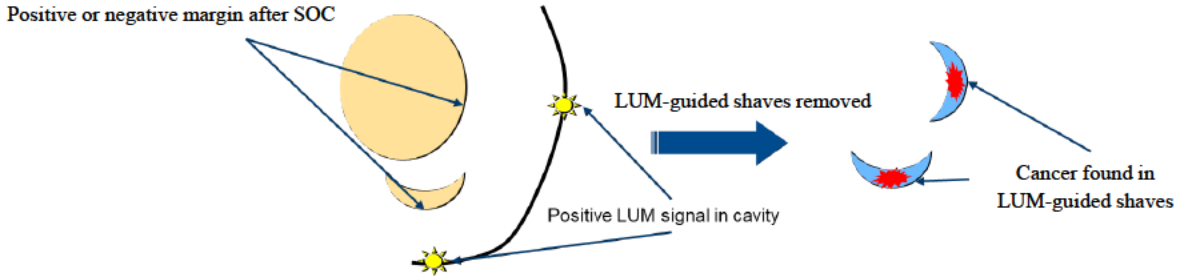
- Patient reported outcomes measures to evaluate patient's perceived breast satisfaction before surgery and at 3 timepoints after surgery.

7.1.2.1 Removal of Residual Cancer Primary Endpoint

Removal of residual cancer was the primary endpoint (as depicted in Figure 14). Mathematically, it is defined as:

$$\frac{\#\ patients\ with\ residual\ cancer\ found\ in\ at\ least\ one\ LUM-guided\ shave}{Total\ number\ of\ patients}$$

Figure 14: Depiction of Removal of Residual Cancer Endpoint

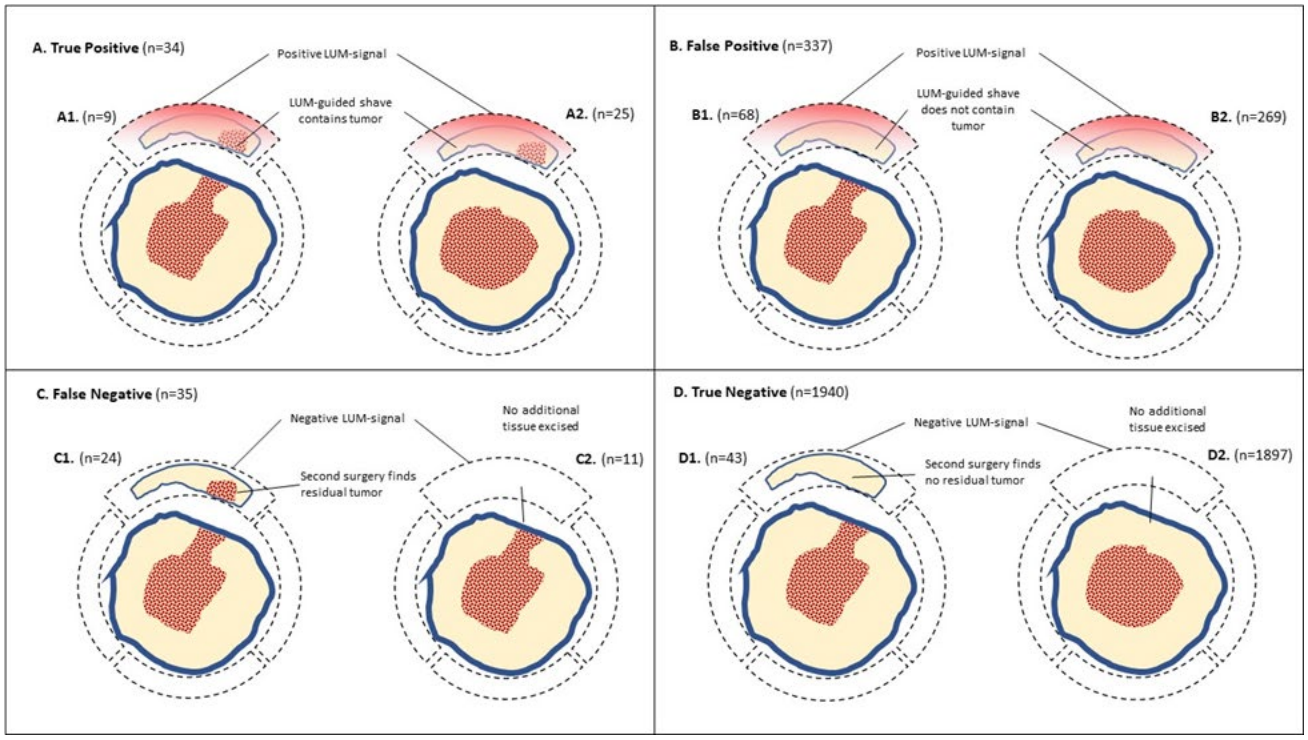


The performance goal for this endpoint was agreed to by the FDA and chosen based on published results for estimates of local recurrence before and after adjuvant radiation were used, assuming that most local recurrences are a consequence of residual cancer left behind during the initial surgery.[3–5] A meta-analysis was conducted on approximately 28,000 patients to support the consensus guideline for margin in 2014 from SSO-ASTRO. This analysis reported an overall recurrence rate of 5.3% for patients undergoing lumpectomy and receiving whole breast radiation therapy (including patients with positive and negative margins).[27] Based on this 5.3% recurrence, the Sponsor proposed that a **>3%** performance goal for the lower bound of the 95% CI (more than half of the 5.3%) for this co-primary endpoint would equate to an important clinical impact upon minimizing the risk of incomplete cancer resection.

7.1.2.2 Diagnostic Performance: Sensitivity and Specificity

The system diagnostic accuracy is measured by the combination of sensitivity and specificity on a per-tissue basis. Because a corroborative margin was not excised when a LUM-negative image was obtained in the lumpectomy cavity orientation, the study followed a hierarchical approach to determine the truth standard as depicted in Figure 15. LUM images (positive or negative) from each lumpectomy cavity orientation were compared with histology of the adjacent tissue to classify the image as true positive (Panel A), false positive (Panel B), false negative (Panel C), or true negative (Panel D). *Positive LUM images* (Panels A and B) were compared with the pathology assessment of the guided shave, whether the prior margin in that orientation was assessed by pathology to be positive (Panels A1 and B1) or not (Panels A2 and B2). *Negative LUM images* (Panels C and D) were compared with the pathology assessment of tissue excised from the imaged orientation at a second surgery if indicated (Panels C1 and D1) or inferred from the prior excised lumpectomy margin at that orientation if no additional tissue was excised (Panels C2 and D2). Sensitivity was defined as the proportion A/(A+C), and specificity was defined as the proportion D/(D+B).

Figure 15: **Definition of Truth Standard to Evaluate the System Diagnostic Performance of the LUM System**



LUM-guided surgery readings (positive or negative) from each lumpectomy cavity orientation were compared with histopathology of the adjacent tissue to classify the LUM signal as true positive (Panel A), false positive (Panel B), false negative (Panel C), or true negative (Panel D). *Positive LUM-guided readings*: (Panels A and B) were compared with histopathology of the guided shave whether the prior margin in that orientation was positive (Panels A1 and B1) or not (Panels A2 and B2). *Negative LUM-guided readings:* (Panels C and D) were compared with histopathology of tissue excised from the imaged orientation at a second surgery (Panels C1 and D1) or with the prior excised lumpectomy margin at that orientation if no additional tissue was excised (Panels C2 and D2).
Source: Smith, et. al. 2023[47]

Based on Lumicell's prior feasibility study, SoC margin pathology achieved a sensitivity of 38.2% in predicting residual cancer in the lumpectomy cavity; however, this pathology assessment is completed several days after surgery. Given that the LUM System provides the added benefit of real-time cavity assessment during the initial surgery, the FDA agreed that the LUM System's performance goal for sensitivity should be at least as good as pathology, with a lower bound of **> 40%** (rounded up from 38% to 40%).

Lumicell's prior data also demonstrated tissue-level specificity with a lower bound of 68%, resulting on an average of ~1 LUM-guided shave accounting for ~10% of the total tissue resected. Based on other studies that investigate the amount of tissue removed by comprehensive shaves, this amount of additional tissue resected seemed to have no negative impact on patients cosmesis or complication rates.[13,50] Thus, to ensure similar performance in the Pivotal Study, the performance goal selected for the lower bound of the tissue-level specificity is **> 60%**.

Beyond their value as individual measures, the performance goals for sensitivity and specificity can also be combined to generate a Youden Index ([sensitivity + specificity]-1), which if > 0, demonstrates a non-random diagnostic performance.

7.1.3 Statistical Analysis Plan

The 3 efficacy co-primary endpoints described above were required to meet prespecified performance goals for the declaration of success for this Pivotal Study.

For the primary endpoint of Removal of Residual Cancer, success was declared by the true percentage of patients in whom at least 1 LUM-guided shave contained cancer after SoC procedure, as confirmed by pathology examination, and was equal to or greater than 3% at the lower bound of the 95% CI.

For the co-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%. Because multiple readings were obtained for each patient, the sensitivity and specificity calculations were reported by using the Generalized Estimating Equations (GEE) method to account for potential intra-patient bias.

7.1.4 Patient Disposition

Eligible patients who met study inclusion criteria at screening were considered as enrolled only after administration of LUMISIGHT. The study population flow chart (Figure 16) presents an overview of the disposition of patients who were enrolled and participated in the study. Any patient who provided consent but did not receive study treatment (LUMISIGHT) was considered a screen failure.

Patient disposition data is provided in Table 6. A total of 490 patients consented as eligible study participants of which 84 patients (17%, 84 out of 490 patients) did not meet eligibility criteria and were considered ‘screen failures. Thus, 406 patients were injected with LUMISIGHT and are included in the safety population.

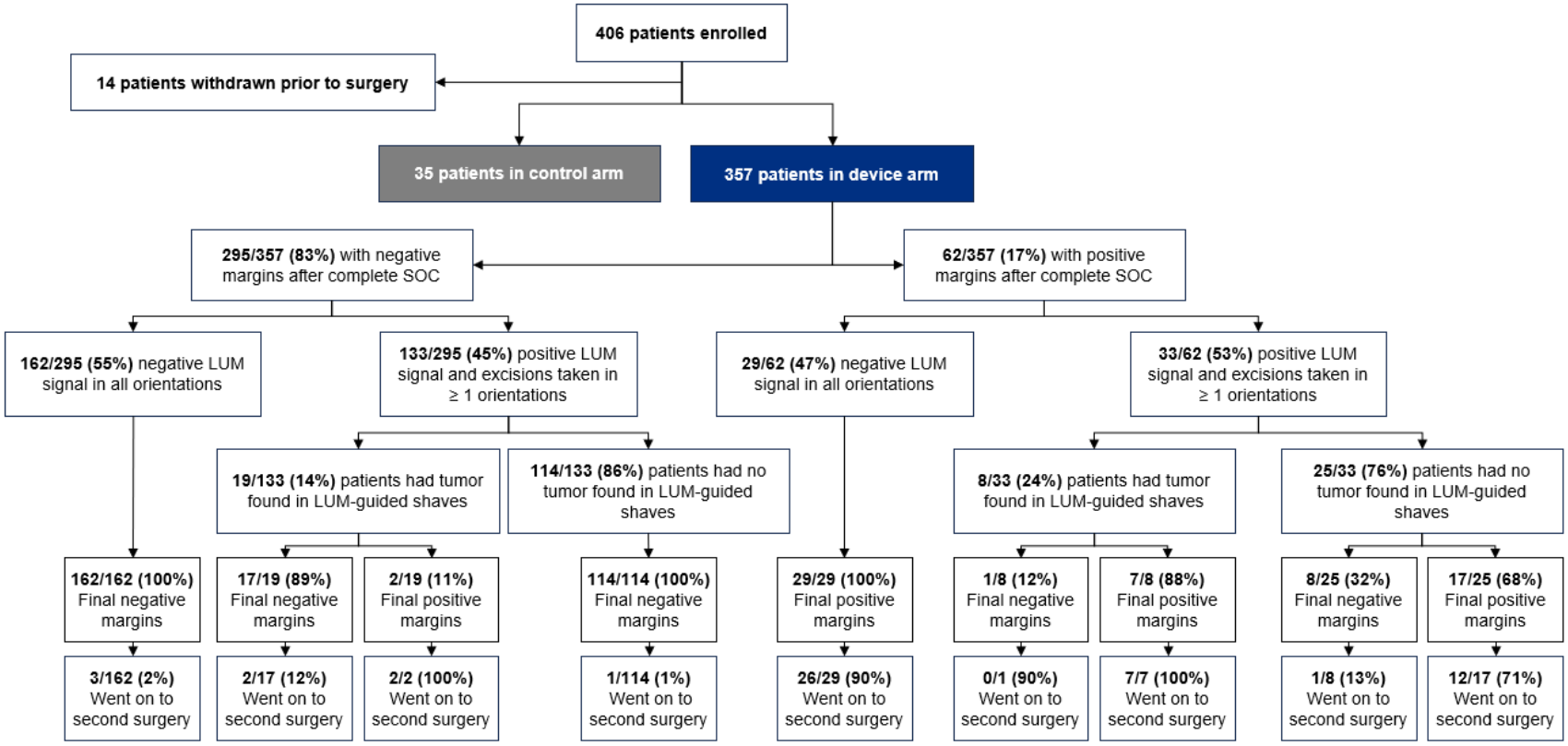
Fourteen patients were withdrawn from the study after injection of LUMISIGHT but before randomization (see Table 7 for a description of these cases). Patients were considered withdrawn if, after enrollment, the study intervention (LUMISIGHT injection or imaging using the Lumicell DVS) was discontinued prior to completion. Data collected from withdrawn patients was only used for analysis if the requirements for inclusion in the analysis population were met and consent for data use was not withdrawn. Therefore, as seen in the Population Flow Chart in Figure 16, a total of 392 patients were randomized to either the Lumicell DVS Arm (N = 357) or Control Arm (N = 35). The evaluation of efficacy was based only on those patients randomized to the Lumicell DVS arm: 62/357 (17%) of patients had positive margins and 295/357 (83%) of patients had negative margins after completing SoC BCS.

Of the 62 patients with positive margins after SoC, 8 patients had additional tumor found in LUM-guided shaves. Of the 295 patients with negative margins after SoC, 19 patients had

tumor found in LUM-guided shaves. This was tumor that was otherwise missed by SoC BCS.

Of the 62 patients with positive margins after SoC, 9 (14.5%) patients were converted to negative margins intraoperatively (1 patient had tumor found in the LUM-guided shaves and 8 others did not find tumor in the LUM guided shaves).

Figure 16: Pivotal Study Population Flow Chart



*See Table 7 below for reasons leading to withdrawal.

Table 6: Patient Disposition in the Pivotal Study

Disposition	Number of Patients
Patients with Informed Consent Form signed	490
Screen Failures n (%)	84 (17%)
Patients having LUMISIGHT injected (Safety Analysis Population) n (%)	406 (83%)
Patients withdrawn after the injection but prior to randomization n (%)	14 (3%)
Patients randomized to the device group (Efficacy Population) n (%)	357 (73%)
Patients in device group withdrawn before completing LUM System imaging n (%)	1 (0.2%)
Patients completed with LUM System imaging	356 (73%)
Patients randomized to Control group n (%)	35 (7%)

Table 7: Reasons for Patient Withdrawal

Disposition	Reasons for Failed Completion of the Study	Number of Patients Withdrawn, n (%) (N = 406)
Withdrawn after injection but prior to randomization	Adverse event	7 (2%)
	Device/system issue	2 (0.5%)
	Physician decision: incision too small for device	1 (0.2%)
	Protocol deviation: blue dye injection	3 (0.7%)
	Protocol deviation: prior ipsilateral procedure	1 (0.2%)
Withdrawn after randomization	Device/system issue	1 (0.2%)

7.1.5 Demographics

Patient demographics are presented in Table 8. Overall, demographic characteristics data of the enrolled populations were generally representative of the US population of newly diagnosed patients with breast cancer (see table in Appendix 12.5). The median age of breast cancer diagnosis in the population represented by Surveillance Epidemiology and End Results (SEER) data is 63 years, similar to the median age of patients in this Pivotal Study (62 to 64 years of age across the study population groups). Most of the participants in this trial were non-Hispanic white women. The Hispanic population was also low at 3% but similar to other large breast cancer lumpectomy trials that enrolled the same proportion of Hispanic women.[50] The proportion of Black women who participated was small (6%). Lumicell recognizes the importance of diversity in clinical trials and expected to enroll a diverse and representative group of women by selecting a geographically diverse set of medical centers to participate in this trial, as rates of breast cancer incidence vary across the U.S.[30] Lumicell engaged 10 academic

medical centers and 4 non-academic hospitals throughout the country in attempt to achieve a diverse and representative recruitment.

Additionally, informed consent documents in many languages were available to potential participants.

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 8: Patient Demographics in Pivotal Study

Characteristics	LUMISIGHT Injected (Safety Analysis Population) (N = 406)	Efficacy Population (N = 357)	Control Group (N = 35)
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)
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)

Max: Maximum; Min: Minimum

7.1.6 Disease Characteristics

The tumor characteristics for the Pivotal Trial populations are shown in Table 9. Also, the tumor characteristics data of the participants in this study were representative of the US population of newly diagnosed patients with breast cancer (see table in

Appendix 12.5). The median tumor size was 1.5 cm in the safety and efficacy study populations (i.e., largest dimension of tumor in the main lumpectomy specimen) and 1.9 cm in the control population. These data were comparable to the published literature on tumor size in similar populations.[51]

The tumor histology data showed more than 70% of subjects across the population groups had tumors of IDC or DCIS origin which is comparable to data in published literature that showed IDCs contributed to approximately 80% of the newly diagnosed population.[52]

Table 9: Tumor Characteristics

Characteristics	Safety Analysis Population (N = 406)	Efficacy Population (N = 357)	Control Population (N = 35)
Mammographic Breast Density			
Almost Entirely Fatty	5 (1.2%)	5 (1.4%)	0
Scattered Areas of Fibroglandular Density	220 (54.2%)	196 (54.9%)	20 (57.1%)
Heterogeneously Dense	163 (40.1%)	140 (39.2%)	13 (37.1%)
Extremely Dense	13 (3.2%)	11 (3.1%)	2 (5.7%)
Not Reported	5 (1.2%)	5 (1.4%)	0
Palpability			
Palpable Mass	100 (24.6%)	85 (23.8%)	11 (31.4%)
No Palpable Mass	306 (75.4%)	272 (76.2%)	24 (68.6%)
Not Reported	0	0	0
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			
DCIS Only	64 (15.8%)	56 (15.7%)	6 (17.1%)
IDC ± DCIS	294 (72.4%)	259 (72.5%)	25 (71.4%)
ILC ± DCIS	45 (11.1%)	39 (10.9%)	4 (11.4%)
IDC + ILC	3 (0.7%)	3 (0.8%)	0
Not Reported	0	0	0
Receptor Status			
ER (+)	378 (93.1%)	335 (93.8%)	30 (85.7%)
PR (+)	311 (76.6%)	272 (76.2%)	28 (80.0%)
HER2 (+)	18 (4.4%)	17 (4.8%)	1 (2.9%)
Triple Negative			
Yes	12 (3.0%)	9 (2.5%)	2 (5.7%)
No	394 (97.0%)	348 (97.5%)	33 (94.3%)

Characteristics	Safety Analysis Population (N = 406)	Efficacy Population (N = 357)	Control Population (N = 35)
Not Reported	0	0	0
Lymph Nodes			
Lymph Node (+)	59 (14.5%)	52 (14.6%)	7 (20.0%)
Lymph Node (-)	259 (63.8%)	237 (66.4%)	22 (62.9%)
No Lymph Node Biopsy	74 (18.2%)	68 (19.0%)	6 (17.1%)
Lymph Node Status Not Reported	14 (3.4%)	0	0

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; PR: Progesterone receptor

7.1.7 Primary Endpoints Results

7.1.7.1 Removal of Residual Cancer

The results for the primary endpoint of Removal of Residual Cancer guided by the Lumicell DVS demonstrated that 27 out of 357 patients randomized to the Lumicell DVS Arm had residual cancer found and removed in at least 1 LUM-guided shave (7.6%; 95% CI: 5.0%, 10.8%) and confirmed by pathology. The performance goal for this endpoint was met successfully for the Lumicell DVS with a lower bound CI of 5.0%, which was greater than the preset performance goal of 3% (Table 10)

Table 10: Removal of Residual Cancer Endpoint

Primary Endpoint	
Ratio of patients who have residual cancer found in at least one LUM-guided shave among all patients in the Device Arm (patient-level) % (n/N)	7.6% (27/357) 95% CI: 5.0%, 10.8%

CI: Confidence interval
Note: CI calculated using Binomial Clopper-Pearson method

Residual cancer removed in LUM-guided shaves included Grade 3 histology in 13 of 27 patients, and residual cancer ≥ 1 mm in size in 18 of 27 patients (Table 11).

Of these 27 patients, 22 had residual cancer removed in LUM-guided shaves corresponding to negative margin orientations:

- 19 patients with all negative SoC margins – these patients would have completed their SoC BCS with cancer remaining in the lumpectomy cavity and likely would not have received a second surgery because the SoC pathology-determined margins were negative.
- 3 patients with SoC positive margins had residual cancer removed guided by the Lumicell DVS from orientations with a SoC negative margin that potentially would not be addressed in a second surgery.

In these patients, the LUM System detected and guided the removal of residual cancer that otherwise remained undetected by the SoC procedure. Hence, the combination of LUMISIGHT and the Lumicell DVS was highly beneficial to these patients in removing cancerous tissue and potentially reducing long-term local disease progression.

Table 11: Summary of Patients with Residual Cancer Removed in LUM-Guided Shaves by Largest Tumor Dimension, Tumor Grade, Age, and SoC Margin Status (Sorted by Age)

Age	Primary Tumor Histology	Tumor Histology in LUM-Guided Shave	Largest Tumor Size in LUM-Guided Shave (mm)	Tumor Grade	Estrogen Receptor (+ or -)	Margin Status After SoC BCS
Detection of Residual Invasive Cancer						
51	IDC + DCIS	IDC	1.5	3	+	Negative
52	ILC	ILC	4	2	+	Negative
65*	ILC	ILC	5	2	+	Positive
71	IDC	IDC	NR	3	+	Negative
71	ILC	ILC	6.5	2	+	Negative
77	IDC + DCIS	IDC + DCIS	NR	1	+	Negative
Detection of Residual DCIS						
36	IDC + DCIS	DCIS	2	3	+	Negative
41	DCIS	DCIS	NR	3	+	Positive
42	IDC + DCIS	DCIS	NR	3	+	Negative
47	IDC + DCIS	DCIS	1	3	+	Negative
52	IDC + DCIS	DCIS	13	2	+	Negative
53	IDC + DCIS	DCIS	1.5	1	+	Negative
55	DCIS	DCIS	NR	3	+	Positive
56	DCIS	DCIS	2	2	+	Positive
58	IDC + DCIS	DCIS	NR	3	-	Negative
58	IDC + DCIS	DCIS	2	3	+	Negative
58	IDC + DCIS	DCIS	11	3	+	Negative
59	ILC + DCIS	DCIS	NR	2	+	Negative
60	IDC + DCIS	DCIS	1	2	+	Negative
60*	DCIS	DCIS	7	2	+	Positive
65	IDC + DCIS	DCIS	2	2	+	Negative
65	IDC + DCIS	DCIS	NR	3	-	Positive
66	DCIS	DCIS	7	3	+	Negative
66*	DCIS	DCIS	8	2	+	Positive
67	DCIS	DCIS	0.1	2	+	Positive
70	IDC + DCIS	DCIS	2	3	+	Negative
76	IDC + DCIS	DCIS	11	2	+	Negative

Age	Primary Tumor Histology	Tumor Histology in LUM-Guided Shave	Largest Tumor Size in LUM-Guided Shave (mm)	Tumor Grade	Estrogen Receptor (+ or -)	Margin Status After SoC BCS

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; DCIS: Ductal carcinoma in situ; NR: Not reported in case report form.
*These patients had positive SoC margins with residual cancer removed in a LUM-guided shave from a negative margin orientation.

7.1.7.2 Diagnostic Performance

The diagnostic performance of the Lumicell DVS to detect and guide the removal of residual cancer was evaluated by the primary endpoints of tissue-level sensitivity and tissue level specificity. For this analysis of diagnostic performance, a hierarchical approach was used to determine the truth standard for the tissue evaluations, with data presented in Figure 15, leading to the 2x2 contingency table for tissue-level sensitivity and specificity (Table 12).

Table 12: Contingency Table for Tissue-level Sensitivity and Specificity

	Hierarchical Truth Standard		Total
	Positive	Negative	
LUM-Positive Signal	34	337	371
LUM-Negative Signal	35	1940	1975
Total	69	2277	2346

Point estimates for the primary endpoints of tissue-level sensitivity and tissue-level specificity are presented in Table 13. The diagnostic performance endpoints based on the GEE approach[a] were 49.1% for tissue-level sensitivity (34 out of 69 truth standard positives; 95% CI: 36.4%, 61.9%) and 86.5% for tissue-level specificity (1,940 out of 2,277 truth standard negatives; 95% CI: 84.5%, 88.3%).

The sensitivity endpoint did not meet the preset performance goal of 40.0% by 3.6 percentage points at the lower bound of the 95% CI (i.e., 36.4%), whereas the specificity endpoint successfully met and exceeded the preset performance goal of 60.0% by 24.5 percentage points (i.e., 84.5%) at the lower bound of the 95% CI (two-sided 95% CI; Table 13).

The diagnostic performance of the LUM System had a Youden Index (sensitivity + specificity -1) of 0.36 (95% CI: 0.21, 0.50; with the entire confidence interval > 0; Table 13). This indicated that the LUM System DVS diagnostic performance was better than a random diagnostic tool.

[a] A single patient can generate multiple data points (at least 1 per orientation). Thus, sensitivity and specificity were measured at a tissue-level. To address potential within-patient correlation, the GEEs were used to estimate the sensitivity and specificity along with the two-sided 95% confidence interval.

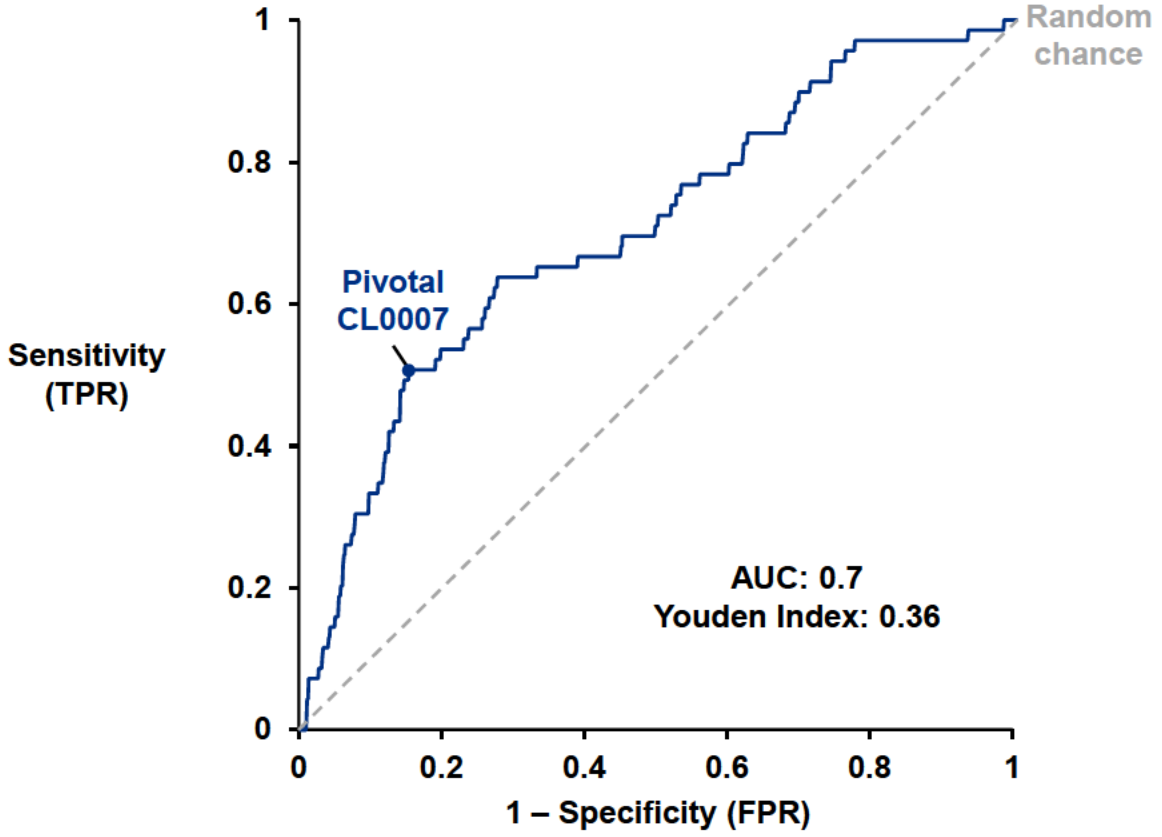
Table 13: Tissue-Level Sensitivity and Specificity

Metric	Efficacy Population (N = 356)
Generalized Estimating Equations Method (method used to evaluate performance goal criteria)	
Sensitivity	49.1% 95% CI: 36.4%, 61.9%
Specificity	86.5% 95% CI: 84.5%, 88.3%
Youden Index	0.36 95% CI: 0.21, 0.50

CI: Confidence interval

To further investigate the informative nature of the LUM System, an ROC curve was generated with the Pivotal Study data. The resulting ROC curve is shown in Figure 17 and shows the trade-offs between sensitivity and specificity for the LUM System tumor detection algorithm threshold setting. The ROC AUC provides a measure of the overall performance of the system to accurately classify truth standard positive and truth standard negatives. An AUC of 0.5 (area under the dashed line in Figure 17 indicates a system that provides no discrimination (random information), while an AUC of 1.0 indicates a perfect classification system. The ROC AUC for the LUM System based on Pivotal Study data is 0.7, suggesting a 70% likelihood of correctly classifying residual cancer present or not present in the lumpectomy cavity.

Figure 17: Receiver Operating Curve for the Tumor Detection Algorithm Based on Pivotal Study Data



AUC: Area under the curve; FPR: False positive rate; ROC: Receiver operating characteristics; TPR: True positive rate or sensitivity
Tissue images and pathology data were used to build the ROC curve describing the LUM System performance. The gray circle indicates the resulting operating point in the Pivotal Study that produced a 49.1% sensitivity, 86.5% specificity, and 0.36 Youden Index. The AUC for this ROC is 0.7 indicating that the system has a 70% likelihood of correctly classifying residual cancer present or not present in the lumpectomy cavity.

The diagnostic performance of the LUM System failed to meet the sensitivity endpoint; however, it successfully met the specificity endpoint. It is speculated that the study design, in which some imaging results were compared only against the prior margin because no additional tissue was removed, could have impacted this endpoint. Regardless, the LUM System performance clearly provided information to surgeons to either take or not take an additional shave with a resulting Youden Index of 0.36 and an ROC AUC of 0.7 demonstrating that the predictive ability of the system is better than taking randomly selected shaves.

With these diagnostic performance results, the primary endpoint of removal of residual cancer was met (Section 7.1.7.1) as well as enabling the conversion of positive margins after SoC to final negative margins as described below. Even with a false positive rate of 13.5% (1-specificity) that led to excision of some shave margins that did not contain tumor, patient reported surveys suggest that the additional LUM-guided tissue removed

had no significant impact on patient's perceived cosmesis (Section 7.1.8.2). In summary, the diagnostic performance addressed the unmet need of removal of residual cancer left behind after the SoC procedure and conversions to final negative margins with no significant impact on patient's perceived cosmesis.

7.1.8 Secondary Endpoints Results

7.1.8.1 Conversion of Positive SoC Margins to Final Negative Margins by Excising LUM-Guided Shaves (Patient-Level)

The results for the following endpoints are presented in Table 14.

In the Pivotal Study, 62 (17.4%) patients had positive margins after the SoC lumpectomy, of which 9 were converted to final negative margins by excising LUM-guided shave. That is, by using the LUM System the positive margin rate was reduced by 15% (9 out of 62 patients; 95% CI: 6.9%, 25.8%; Table 14). Out of these 9 patients, 8 were spared a second surgery, but 1 patient had a second surgery even with final negative margins, driven by a decision from the tumor board that evaluated this case.

Of the 9 patients converted to final negative margins by excising LUM-guided shaves, cancer was found in the LUM-guided shave in 1 of these patients. That is, in the remaining 8 patients where a LUM-guided shave was removed, though pathology did not find cancer in the shave, the removal of the shave converted an SoC positive margin to a negative margin, hence potentially avoiding a follow-up surgery that may have not contained cancer either.

As described in Section 4.3, LUMISIGHT is designed to be activated by both cancerous and noncancerous tumor-related cells at the invasive front. Thus, the design of LUMISIGHT will generate false-positives (i.e., tissue with LUM-positive signal but no tumor in the guided shave). However, with this approach a small amount of noncancerous tissue can be removed to help obtain negative margins, even when the LUM-guided shave has no cancer. Furthermore, this result aligns with prior studies that showed no tumor found in 65% of the tissue removed following a positive margin;[13,16] however, the LUM-guided procedure is completed during the initial surgery, potentially avoiding a second surgery in 15% of patients with SoC positive margins.

Table 14: Conversion of Positive Standard of Care Margins by Excising LUM-Guided Shaves

	Efficacy Population (N = 357)
Patients having positive margins after SoC lumpectomy procedure n (%)	62 (17.4%) 95% CI:13.6%, 21.7%
Secondary endpoint: Percent of patients converted from positive margins after SoC lumpectomy procedure to final negative margins by excising LUM-guided shaves n (%)	14.5% (9/62) 95% CI: 6.9%, 25.8%

BCS: Breast conserving surgery; CI: Confidence interval; SoC: Standard of care

7.1.8.2 Average Volume of LUM-Guided Shaves and Contribution to Total Excision Volume

Table 15 summarizes the results for tissue volumes related to the SoC lumpectomy procedure (including SoC shaves), LUM-guided shaves, and their contribution to overall total volume of tissue removed. The results are presented for the entire efficacy population (N = 357) and for the subpopulation of patients that had at least 1 LUM-guided shave (N = 166).

The mean (± standard deviation [SD]) total SoC volume (prior to using the LUM System) removed in the efficacy population was 89.0 cm^3 (± 93.7 cm^3; Table 15). The large standard deviation reflects the variability of multiple factors such as tumor size, tumor mass characteristics, and surgeon's practice in deciding how much tissue to remove during the SoC procedure.

The mean total LUM-guided shave volume was 10.1 cm^3 (± 17.5 cm^3) across the efficacy population. The mean contribution of this tissue removed constituted 9.4% (±14.1%) of the total volume or resection (Table 15).

When at least 1 LUM-guided shave was removed, the mean LUM-guided shave volume was 21.8 cm^3 (± 20.1 cm^3). The mean contribution of this tissue removed constituted 20.3% (± 14.5%) of the total volume or resection (Table 15).

The average number of LUM-guided shaves removed per patient across the efficacy population was 1.0 ± 1.4. For the sub-population consisting of patients with at least 1 LUM-guided shave removed, the average number of LUM-guided shaves removed was 2.2 ± 1.4.

Table 15: Summary of Tissue Volumes: Lumpectomy, SoC Shaves, LUM-Guided Shaves, and Contribution to Total Tissue Volume

	Efficacy Population (N = 357)	Efficacy Population with At Least 1 LUM-Guided Shave Removed (N = 166)
Lumpectomy volume (cm^3)		
Mean (SD)	74.9 (76.5)	70.5 (55.9)
SoC Shave Volume (cm^3)		
Mean (SD)	14.1 (36.7)	16.3 (24.0)
SoC Total Volume (cm^3)		
Mean (SD)	89.0 (93.7)	86.8 (70.0)
Secondary Endpoint: LUM-guided shave volume (cm^3)		
Mean (SD)	10.1 (17.5)	21.8 (20.1)
Total Volume (cm^3)		
Mean (SD)	99.1 (97.3)	108.6 (79.0)
Secondary Endpoint: Ratio of LUM-guided shaves contributing to total volume		
Mean (SD)*	9.4% (14.1%)	20.3% (14.5%)

SD: Standard deviation, SoC: Standard of care
*The mean contribution of LUM-guided shaves to total volume is reported by calculating the contribution to each patient and then obtaining the overall mean, not by dividing the mean LUM-guided shave by the mean total volume.

7.1.8.3 Patient-Level Analysis of Sensitivity and Specificity

The sensitivity and specificity results presented in Section 7.1.7.2 address the diagnostic performance of the LUM System at the tissue level and includes multiple readings for each patient (there are 6 individual lumpectomy cavity orientations imaged by the LUM System). However, we investigated extrapolating tissue-level results to patient-level results with 2 different approaches described in Table 16. The differences between these 2 approaches are due to the definitions of true positives and false negatives.

In Approach 1, a true positive patient has at least 1 tissue-level positive reading and a false negative patient has at least 1 tissue-level false negative reading with no additional true positive readings. Approach 2 uses a narrower definition for the patient-level sensitivity analysis, in which a true positive patient has at least 1 tissue-level positive reading but no tissue-level false negatives and a false negative patient has at least 1 tissue-level false negative reading, regardless of true positive readings.

Both approaches used the same definitions for true negatives and false positives: true negatives patients have only tissue-level true negative readings and false positive patients have at least 1 tissue-level false positive, but no tissue level true positives or false negatives.

Approach 1 captures patients that benefited from having residual cancer removed that was left behind during the SoC procedure and resulted in a per-patient sensitivity of 54% (95% CI: 40%, 68%) (Table 17). That is, 54% of the patients with residual cancer after the SoC lumpectomy procedure had at least some residual cancer removed due to the LUM System. Approach 1 included 5 true positive patients with both LUM-guided residual cancer removal and at least 1 tissue-level false negative. Therefore, under the narrower definition of Approach 2, these 5 patients were instead classified as false negatives with a patient-level sensitivity of 44% (95% CI: 30%, 59%).

It is important to note that the proposed indication for use for the LUM System is as an adjunct to the SoC lumpectomy procedure and not intended to replace any of the SoC procedures. As such, any false negative patients after LUMIIGHT is approved will still undergo all the necessary SoC procedures, including second surgeries when needed.

The patient-level specificity was 58% (95% CI: 52%, 63%) and applied to both approaches (same definitions for both). That is, approximately 42% of the patients had at least 1 LUM-guided shave that had no cancer. However, as described above, 9 of these patients benefited by having their positive margins converted to final negative margins by excising this LUM-guided shave in real-time.

Table 16: Definitions for the Patient-Level Sensitivity and Specificity Analysis

	Approach 1	Approach 2
True Positive Patient	Patient who had at least 1 tissue-level true positive	Patient who had at least 1 tissue-level true positive and no false negatives
False negative Patient	Patient who had at least 1 tissue-level false negative and no true positives	Patient who had at least 1 tissue-level false negative
True Negative Patient	Patient who had at least 1 tissue-level true negative and no true positives, no false positives, and no false negatives	
False Positive Patient	Patient who had at least 1 tissue-level false positive and no true positives and no false negatives	

Table 17: Patient-Level Sensitivity and Specificity Results

Metric	Approach 1: Patient-Level Performance N = 356*	Approach 2: Patient-Level Performance N = 356*
Truth Standard Positives	50	50
Truth Standard Negatives	306	306
True Positives	27	22
True Negatives	176	176
Sensitivity	54% (95% CI: 40%, 68%)	44% (95% CI: 30%, 59%)

Metric	Approach 1: Patient-Level Performance N = 356*	Approach 2: Patient-Level Performance N = 356*
Specificity	58% (95% CI: 52%, 63%)	58% (95% CI: 52%, 63%)

*Out of the 357 patients in the treatment arm, 1 patient did not complete the LUM imaging procedure and was excluded from this analysis.

7.1.9 Exploratory Endpoint: Patient Reported Outcomes Measures and Impact on Cosmesis

7.1.9.1 Patient Reported Outcomes Measures Data Collection

The previous section presented the contribution of LUM-guided shaves to the overall lumpectomy resection volume. To explore the impact to the patient's perceived cosmesis from additional tissue removed due to a LUM-guided shave, the Pivotal Study included a pre-defined endpoint to collect PROMs information. This endpoint was designed to be exploratory, as there were many factors that could impact this data, such as the type of surgery performed (i.e., lumpectomy alone or lumpectomy plus oncoplastic surgery) and survey participation rates. Participation in this exploratory study was optional.

The data were collected using the validated survey Breast-Q[53] implemented within the study's EDC (see Appendix 12.11, Table 32 for the questionnaire). Timepoints for survey collection included: pre-surgery (baseline), approximately 2 weeks after surgery (during routine follow-up), 3 months, and 6 months after the lumpectomy. The 6-month follow-up timepoint was added to the study design after enrollment started, therefore, a smaller number of patients completed surveys at the 6-month timepoint.

Table 18 shows the number of patients that agreed to participate and were ultimately compliant in survey completion. Although 255 (72%) patients in the efficacy population agreed to participate in the survey, only 161 of the 357 (45%) patients completed the survey at the pre-surgery timepoint. Survey completion rates were impacted due to diminished in-person follow-up physician visits because of the COVID-19 pandemic, which took place during enrollment into the Pivotal Study. In addition, it is also generally expected to see a decrease in survey completion rates as follow-up time increases.

Table 18: Participation of Patients in the PROMs Optional Endpoint

Time Frame	Number of patients in the efficacy population	Number of patients in the efficacy population that consented to participate in the PROM survey (% of total efficacy population, N = 357)	Number of patients that completed the survey (% of total consented for PROMs)	Number of patients that did not have LUM-guided shaves removed (% of those completed the PROM survey)	Number of patients that had at least 1 LUM-guided shave removed (% of those completed the survey)
Pre-Surgery Time Frame	357	255 (72%)	161 (63%)	84 (52%)	77 (48%)
Follow-up Time Frame			154 (61%)	77 (50%)	77 (50%)
3-Month Time Frame			126 (49%)	58 (46%)	68 (54%)
6-Month Time Frame		147* (42%)	50 (34%)	23 (46%)	27 (54%)

PROM: Patient-reported outcomes measure
*The 6-month data collection timepoint was added to the study design after enrollment had started, thus this timepoint was presented to a smaller pool of study participants.

7.1.9.2 *Comparison of PROM Responses Between Patients with and Without LUM-Guided Shaves Removed*

Distribution of the PROM responses across the groups with and without therapeutic shaves was plotted for each timeframe. The proportions for each level of responses were comparable between the groups. Comparison of the patient satisfaction of lumpectomy with or without therapeutic shave was applied with Item Response Theory[54] with the assumption of all the items equally discriminative of the responded patients. For each timeframe, the responses to all the items from the population were projected with a factor score for each patient. The scaled factor scores (0-100) were compared between the groups with and without the therapeutic shave. For all the timeframes examined, no significant difference was found between the groups with and without LUM-guided shaves (p>0.05, Table 19).

Table 19: Survey Results by Patients With and Without LUM-Guided Shaves

	Device Arm Without LUM-Guided Shaves		Device Arm With LUM-Guided Shaves		T-Test
Description	N	Mean [95% CI]	N	Mean [95% CI]	P-value
Pre-Surgery	84	64.1 [58.7, 69.5]	77	61.3 [56.5, 66.2]	0.45
Follow-up Post-Surgery	77	76.4 [71.4, 81.5]	77	73.9 [69.4, 78.3]	0.45
3-Month Post-Surgery	58	73 [66.6, 79.4]	68	69.4 [64.1, 74.7]	0.38
6-Month Post-Surgery	23	75.4 [63.5, 87.4]	27	71 [62.7, 79.4]	0.53

Although the study was not powered for PROMs to detect statistically significant differences, the data suggest that the patient's perspective on their own breast

satisfaction did not change when LUM-guided shaves were excised. This indicates that the amount of additional tissue removed when using the LUM System does not negatively impact patient's perception of cosmesis.

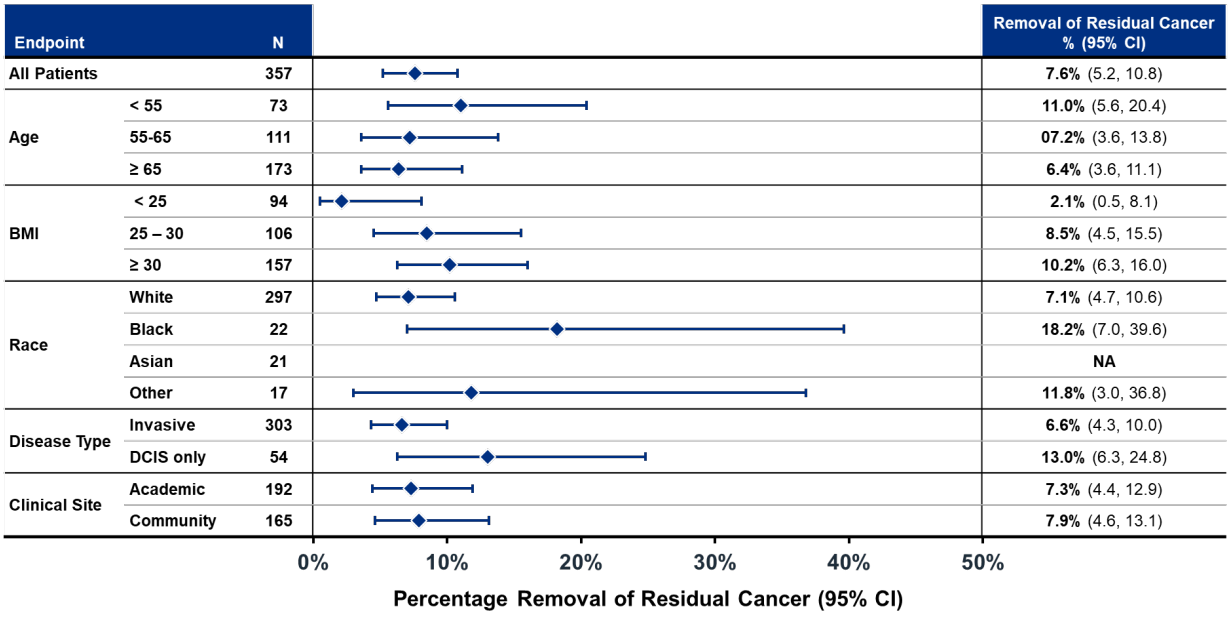
7.2 Subgroup Analysis

Subgroup analyses were performed based on demographics, tumor histology, and whether the sites were academic or non-academic institutions. A total of 5 subgroup analyses were performed for each of the co-primary endpoints. Due to the multiplicity nature of the analysis, the type I error rate alpha for individual analysis used was 0.01 to achieve overall error rate at 0.05 according to Bonferroni correction.[55]

The results of these analyses were balanced for most subgroups and are shown in Figure 18. The only exception seems to be the BMI < 25 kg/m^2 subgroup with lower rates of removal of residual cancer, sensitivity, and specificity. However, this subgroup analysis was not powered to determine the significance in difference between the BMI subgroups. There was no significant difference in the rate of removal of residual cancer, sensitivity, and specificity found between the other subgroups at an $\alpha = 0.01$. Of note, the Asian subgroup had no residual cancer removed, and due to the low number of truth standard positives (N = 4), the sensitivity could not be calculated (NC in Figure 18).

Figure 18: Subgroup Analyses Results

A. Removal of Residual Cancer Subgroup Analysis



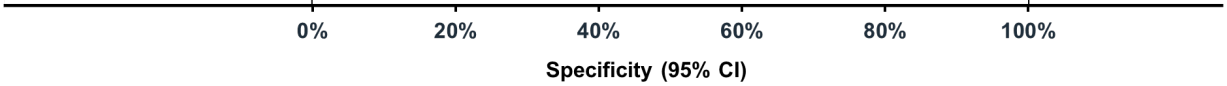
B. Sensitivity Subgroup Analysis

Endpoint		N	Sensitivity % (95% CI)
All Patients		69	**49.1%** (36.4, 61.9)
Age	< 55	21	**53.3%** (30.1, 75.3)
	55-65	21	**47.2%** (26.1, 69.3)
	≥ 65	27	**47.3%** (28.4, 67.0)
BMI	< 25	13	**20.7%** (5.2, 55.3)
	25 – 30	26	**45.9%** (25.1, 68.1)
	≥ 30	30	**65.0%** (47.2, 79.5)
Race	White	53	**49.7%** (35.3, 64.1)
	Black	8	**72.4%** (35.1, 92.7)
	Asian	4	**NA**
	Other	4	**50.0%** (12.3, 87.7)
Disease Type	Invasive	43	**59.8%** (42.6, 74.8)
	DCIS only	26	**30.2%** (15.9, 49.7)
Clinical Site	Academic	39	**47.3%** (30.4, 64.9)
	Community	30	**51.5%** (33.6, 68.9)

Sensitivity confidence intervals were calculated using GEE approach.

C. Specificity Subgroup Analysis

Endpoint		N	Specificity % (95% CI)
All Patients		2,277	**86.5%** (84.5, 88.3)
Age	< 55	464	**85.1%** (79.2, 89.5)
	55-65	717	**84.2%** (80.5, 87.3)
	≥ 65	1,096	**88.6%** (85.9, 90.9)
BMI	< 25	599	**82.9%** (78.1, 86.9)
	25 – 30	681	**86.6%** (93.1, 89.5)
	≥ 30	997	**88.5%** (85.5, 91.0)
Race	White	1,876	**87.6%** (85.4, 89.5)
	Black	142	**86.3%** (77.6, 92.0)
	Asian	142	**78.8%** (68.6, 86.3)
	Other	117	**78.1%** (65.2, 87.1)
Disease Type	Invasive	1,959	**86.8%** (84.6, 88.7)
	DCIS only	318	**84.8%** (78.5, 89.5)
Clinical Site	Academic	1,216	**85.0%** (82.0, 87.5)
	Community	1,061	**88.3%** (85.4, 90.7)



Specificity confidence intervals were calculated using GEE approach.
CI: Confidence interval; GEE: Generalized Estimating Equations

7.3 Efficacy Conclusions

The evaluation of efficacy of the LUM System as an adjunct to the SoC lumpectomy procedure was based on the analysis of the efficacy endpoint results in Pivotal Study CL0007.

In this study, the efficacy results demonstrated success in detecting residual cancer and guiding the removal of the cancerous tissue that would have otherwise remained undetected after completing their SoC BCS in 27 patients (7.6%; 27 out of 357 patients; 95.0% CI: 5.0%, 10.8%; Section 7.1.7.1), thereby surpassing the co-primary endpoint's performance goal of 3%. Residual cancer removed in LUM-guided shaves included Grade 3 histology in 13 of 27 patients, and residual cancer ≥ 1 mm in size in 18 of 27 patients (Table 11).

The diagnostic performance of the LUM System also successfully met the specificity endpoint and exceeded the preset performance goal of 60% by 24.5 percentage points, though it also failed to meet the sensitivity endpoint of 40% by 3.6 percentage points. However, the LUM System performance clearly provided non-random information to surgeons to either take or not take an additional shave with a resulting Youden Index of 0.36 and an ROC AUC of 0.7. These results demonstrate that the predictive ability of the system is better than randomly taking selected shaves.

In addition, the use of the LUM System led to the following clinically meaningful results:

- Approximately 15% (9) of patients with pathology-positive margins after SoC BCS resulted in pathology-negative margins after additional LUM-guided shaves (Section 7.1.8.1)
- 22 out of 357 (6.2%) patients had residual cancer removed in LUM-guided shaves from lumpectomy cavity orientations with negative margins after the SoC BCS. Out of these 22, 19 had all negative margins after SoC BCS. That is, these 19 patients would have completed their initial SoC procedure with cancer remaining in the lumpectomy cavity and likely would have not received a follow-up surgery because the SoC margins were negative (Section 7.1.7.1).
- Across the efficacy population, LUM-guided shaves contributed to approximately 9% of the total tissue removed with an average of 1 shave removed per patient. For those with at least 1 LUM-guided shave removed, the tissue accounted for approximately 20% of the total tissue removed with an average of 2 shaves removed per patient (Section 7.1.8.2).
- The exploratory endpoint of patient satisfaction suggests that removal of LUM-guided shaves did not have significant impact on patient's perceived cosmesis, although the study was not powered for this endpoint (Section 7.1.9).

In summary, the LUM System provided breast cancer surgeons with a novel, adjunctive, *in vivo* imaging capability to detect and guide the removal of residual cancer otherwise

left behind during the initial SoC BCS. The LUM System is an interventional tool with demonstrable clinical benefits that improves the current SoC.

8 CLINICAL SAFETY

Summary

- The safety profile of LUMISIGHT and the Lumicell DVS is characterized from 726 patients dosed at 1 mg/kg (703 breast cancer patients and 23 patients with other cancers).
- LUMISIGHT was generally well-tolerated. Hypersensitivity and anaphylaxis events were managed in the pre-operative hospital setting and did not prevent patients from receiving SoC.
- There have been no deaths reported from the use of LUMISIGHT.
- Chromaturia was the most common mild AE in patients (85%), with 24% of patients experiencing an AE other than chromaturia in the Breast Cancer Safety Population 1 mg/kg.
- A total of 4 out of 726 patients reported SAEs related to the LUMISIGHT injection: 1 severe hypersensitivity and 3 anaphylactic reactions, for a rate of 0.6%. These cases were treated immediately at the hospital, fully recovered, and proceeded to have their SoC lumpectomy procedure.
- To further mitigate the risk of hypersensitivity and anaphylaxis, trained medical professionals are instructed to have resuscitation equipment and medication to treat AEs during the administration of LUMISIGHT.

8.1 Treatment Exposure

The safety analysis for this briefing document focuses on all patients dosed at 1 mg/kg, as this is the recommended dose for LUMISIGHT. This data includes 726 cancer patients as follows:

- 703 breast cancer patients
- 23 patients in other cancer indications

Summary data from the cardiovascular safety study in healthy patients (CLP00201) are not included as part of the overall safety population. A total of 32 patients were enrolled in the study with 24 patients randomized to LUMISIGHT and 8 patients randomized to placebo. No deaths or SAEs occurred during the study. No patient was withdrawn from the study due to safety concerns.

8.2 Overall Safety Overview

Table 20 summarizes the AEs observed in the overall safety population dosed at 1 mg/kg. Details on AE identification and classification can be found in Appendix 12.6.

Table 20: Overview of Adverse Events in Patients Dosed at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
Total AEs	633 (87%)
Chromaturia	615 (85%)
Related chromaturia	613 (84%)
AEs other than chromaturia	176 (24%)
Related AEs other than chromaturia	30 (4%)
Life-threatening AEs	2 (0.3%)
Related life-threatening AEs	1 (0.1%)
SAEs	7 (1%)
Related SAEs	4 (0.6%)
AEs leading to discontinuation	8 (1%)
Deaths	0

AE: Adverse event; SAE: Serious adverse event

8.3 Adverse Events

See Appendix 12.6 for details in AE identification and classification.

8.3.1 Common Adverse Events

The most common AEs reported by patients are presented in Table 21.

Table 21: Common Adverse Events (≥ 2% of Patients) at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
All AEs	633 (87%)
AEs other than chromaturia	176 (24%)
Nausea	17 (2%)
Seroma	31 (4%)
Breast pain	22 (3%)
Chromaturia	615 (85%)

AE: Adverse event
Note: Multiple events experienced by 1 patient within a given category are counted once for the patient counts (n).

8.3.2 Adverse Events Related to Treatment

The most common AE related to LUMISIGHT was chromaturia, which was expected because of the blue color of LUMISIGHT (and is common with other approved treatments using blue dyes). These events typically resolved within 24 to 48 hours. The 4 SAEs related to LUMISIGHT in Table 22 are further discussed in Section 8.5.

Table 22: Common Related Adverse Events (≥ 0.5% of Patients) at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
AEs related to LUMISIGHT	**615 (85%)**
Chromaturia	613 (84%)
Hypersensitivity* (includes 4 SAEs)	9 (1%)
Extravasation	4 (0.6%)
Blood creatinine decreased	4 (0.6%)

AE: Adverse event; SAE: Serious adverse event
*Comprised of the following PTs per discussion with the FDA: 4 hypersensitivity, 3 anaphylactic reaction, 1 pruritus, and 1 urticaria.

8.3.3 Time to Onset of Related Adverse Events

Adverse events related to LUMISIGHT, such as hypersensitivity, allergic reactions, and nausea, have been observed at onset during administration or just after finishing administration of LUMISIGHT (up to 10 minutes). One case of urticaria occurred 2 days after LUMISIGHT administration. These were detected and treated immediately by the medical personnel administering LUMISIGHT.

The most common nonserious AE observed, chromaturia, resolved in most cases within 24 to 48 hours with no sequalae reported.

8.3.4 Severity of Adverse Events

8.3.4.1 Severity of Adverse Events

Most AEs were assessed as mild (86%, Table 23). In total, 11 patients (2%) reported severe AEs in the safety population. Six of the patients that had severe AEs were considered unrelated to LUMISIGHT and 5 of the patients had severe AEs considered related to LUMISIGHT (Table 31, Appendix 12.10).

Two patients had life-threatening AEs. One of these patients had life-threatening and severe AEs which were assessed to be unrelated to LUMISIGHT, including life-threatening AEs of acute respiratory failure and somnolence and severe AEs of acute myocardial infarction and hypotension. The other patient experienced a life-threatening anaphylactic reaction that was assessed to be related to LUMISIGHT and is described in Section 8.5.2.1.

Table 23: Severity of Adverse Events in Patients Dosed at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
All AEs	633 (87%)
Mild	621 (86%)
Moderate	56 (8%)
Severe	11 (2%)
Life-threatening	2 (0.3%)

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
Chromaturia	615 (85%)
Mild	608 (84%)
Moderate	1 (0.1%)
Severe	0
Life-threatening	0
Severity not reported but AE was not clinically significant	6 (0.8%)
AEs other than chromaturia	176 (24%)
Mild	135 (19%)
Moderate	55 (8%)
Severe	11 (2%)
Life-threatening	2 (0.3%)
Other AE severity not reported but no clinical significance	5 (0.7%)

AE: Adverse event

8.3.5 Serious Adverse Events

Seven patients in the safety population had SAEs, of which 4 SAEs were related: anaphylactic reactions in 3 patients and hypersensitivity in 1 patient (Table 24). The anaphylactic reactions and hypersensitivity will be discussed further in Section 8.5. Five non-related SAEs occurred in 3 patients.

Table 24: Serious Adverse Events in Patients Dosed at 1 mg/kg

No. of Patients (n [%]) with:	Overall Safety Population (N = 726)
All SAEs	**7 (1%)**
SAEs related to LUMISIGHT	**4 (0.6%)**
Anaphylactic reaction	3 (0.4%)
Hypersensitivity	1 (0.1%)
SAEs not related to LUMISIGHT	**3 (0.4%)**
Breast cellulitis	1 (0.1%)
Vascular pseudoaneurysm	1 (0.1%)
Somnolence	1 (0.1%)
Acute kidney injury	1 (0.1%)
Acute respiratory failure	1 (0.1%)

AE: Adverse event; SAE: Serious adverse event

8.3.6 Adverse Events Leading to Discontinuation

Overall, in the evaluable safety populations, 8 patients experienced AEs leading to study discontinuation (Table 25)[b]. These patients were excluded from the efficacy evaluation per Statistical Analysis Plan.

Table 25: Listing of Patients with Adverse Events Leading to Study Discontinuation—Patients Dosed at 1 mg/kg

Patient	Preferred Term	Severity	SAE
1	Anaphylactic reaction	Life-threatening	Yes
2	Hypersensitivity	Severe	Yes
3	Anaphylactic reaction	Severe	Yes
4	Hypersensitivity	Severe	No
5	Hypersensitivity	Moderate	No
6	Extravasation	Moderate	No
7	Nausea	Moderate	No
8	Extravasation	Mild	No

SAE: Serious adverse event

8.4 Deaths

No deaths have been reported in any of the clinical studies using LUMISIGHT.

8.5 Allergic Reactions and Hypersensitivity Related to LUMISIGHT

A total of 9 patients reported LUMISIGHT-related hypersensitivity reactions out of the 726 patients (1%). These 9 patients included 4 with SAEs (Table 24), including 1 severe hypersensitivity and 3 anaphylactic reactions, for a rate of 0.6% (out of 726 patients). The other 5 patients reported with LUMISIGHT-related hypersensitivity reactions are listed in Table 29.

Administration of LUMISIGHT is performed in the pre-operative area under medical supervision, thus each event was managed immediately with standard interventions. Three of the 4 patients with related serious hypersensitivity events recovered within 1 hour of symptom onset. One patient required admittance to the intensive care unit, and fully recovered the following day.

8.5.1 Premedication

Premedication in the clinical trial was not mandated, as the Sponsor did not want to mask a safety signal. Alternatively, premedication was permitted at the discretion of the treating physician and was used infrequently; only 14 patients (< 4% of the Pivotal trial)

[b] The additional patient that experienced a related SAE of anaphylaxis was not discontinued as the reaction occurred after the complete injection was performed. The patient went on to be randomized and complete SoC surgery as planned and is therefore not listed in Table 25.

were medicated prophylactically with diphenhydramine. There were no hypersensitivity reactions in these 14 patients.

8.5.2 Post-Hoc Review of Related Hypersensitivity Adverse Events

A post-hoc review of the hypersensitivity events by 3 expert allergists was conducted to evaluate the etiology and severity of each hypersensitivity AE. This review is summarized below, separately for the SAEs (N = 4) and non-SAEs (N = 5).

8.5.2.1 Related Hypersensitivity Adverse Events: Serious (N = 4)

Overall, the expert allergist panel agreed with reporting 3 of the 4 events as allergic reactions and agreed with the reported severity in 2 of these 3 (Table 26). See Appendix 12.7 for details on the exert panel review for each case.

- Patient 1: Panel review aligned with the reporting for the anaphylactic event.
- Patient 2: Panel determined that the serious hypersensitivity met the criteria for the coding of a Preferred Term of anaphylaxis and agreed with the severity of this event.
- Patient 3: Panel disagreed with the designation of anaphylaxis, instead, the panel termed this event as a possible allergic reaction and considered it to be moderate (not severe as reported in the trial) (see Appendix 12.8.1 for details from the panel evaluation).
- Patient 4: Panel disagreed with the designation of anaphylaxis, instead the panel termed this event as a moderate vasovagal event (see Appendix 12.8.1 for details from the panel evaluation).

Grading criteria of the Common Terminology Criteria for Adverse Events (CTCAE v. 5.0 model; Appendix 12.6), which are intended for clinical trial reporting and standardization across trials, is not entirely consistent with grading models used in the Allergy clinical setting. The results of the panel review highlight the conservative approach in which allergic events are graded when using the CTCAE criteria, specifically because the CTCAE grading is guided by the interventions used to treat the reaction. The results show that at least 1 event may be misclassified as a hypersensitivity reaction, instead of a vasovagal event.

Table 26: Allergists Assessment of 4 Cases of SAEs Related to LUMISIGHT

Patient	Term	Severity
Patient 1		
Reported in trial	Anaphylaxis	Life threatening
Allergist post-hoc review	Anaphylaxis	Life threatening
Patient 2		
Reported in trial	Hypersensitivity	Severe
Allergist post-hoc review	Anaphylaxis	Severe

Patient	Term	Severity
Patient 3		
Reported in trial	Anaphylaxis	Severe
Allergist post-hoc review	Possible allergic reaction	Moderate
Patient 4		
Reported in trial	Anaphylaxis	Severe
Allergist post-hoc review	Vasovagal event	Moderate

The panel's evaluation determined that it is possible that these SAE were related to LUMISIGHT injection. However, as in most allergic reactions of unknown origin, the true etiology of the reported SAEs may have been confounded. For example, the patient that experienced the most severe anaphylaxis reaction was given cefazolin (antibiotic) 6 minutes prior to the onset of symptoms. Cefazolin is the most common cause of perioperative anaphylaxis in the United States.[56] It is unclear if this concomitant medication may be associated with the adverse reaction. The panelists provided their hypothesis for a possible mode of action leading to these allergic reactions in Appendix 12.8.2.

8.5.2.2 Related Hypersensitivity Adverse Events: Non-Serious (N = 5)

The expert panel of allergists also reviewed the 5 cases that were determined to be non-serious, hypersensitivity events (Appendix 12.8, Table 29). Three of these 5 events were reported as moderate in the clinical studies, and the panel agreed with this determination. One event was reported as mild in severity, and the allergist agreed with this severity determination. One event, reported in the trial as severe, was determined by the panel to meet the criteria of moderate severity. Overall, there was not much difference in the severity of these 5 events graded in the trial compared to the allergist review. For all cases, the allergists reported that a possible allergic reaction related to LUMISIGHT cannot be ruled out; however, an anxiety related event is more likely the cause of the more severe event.

8.6 Safety in Special Populations: Pregnant Women

There are no available data on LUMISIGHT use in pregnant women to inform a drug associated risk of adverse developmental outcomes. Reproductive and developmental toxicity studies in animals have not been performed.

8.7 Risk Mitigations

Based on data collected in this study and assessments from the allergists panel, anesthesiologist, and breast surgeons, the Sponsor has considered revisions to the Prescribing Information (PI) to further mitigate the risk of hypersensitivity and anaphylactic reactions potentially emerging due to LUMISIGHT administration. Proposed revisions to the Prescribing Information communicated to the FDA include:

- Clearly indicate the risk of "life-threatening anaphylaxis" in the Highlights section and the Warnings and Precautions section.
- Advise healthcare providers that before LUMISIGHT administration, obtain history of allergy, hypersensitivity, or prior hypersensitivity reactions.
- Indicate that patients with history of multiple food or drug allergies, or other hypersensitivities may be at an increased risk.
- Specify to always administer LUMISIGHT in healthcare settings and have emergency resuscitation equipment and trained personnel available.
- Instruct that if hypersensitivity reaction is suspected, interrupt injection.
- Monitor patients for 15 minutes after injection.

It is important to consider that LUMISIGHT is administered in the pre-operative hospital setting under the care of medical professionals that are trained to manage allergic reactions. Two relatively common causes of perioperative drug allergy reactions are antibiotics like cefazolin, and blue dyes. Cefazolin is a cephalosporin frequently used as a pre-operative antibiotic and is the most common cause of perioperative anaphylaxis. Cephalosporin antibiotic allergy overall has a prevalence of up to 2%, and cefazolin specifically causes allergic reactions in 0.5% of patients on first exposure to it. Nonetheless, it is used very frequently in general, and 50% of the trial patients in the Pivotal Study were given cefazolin in the pre-operative setting. Additionally, injected blue dyes are known to induce allergic reactions. Allergic reactions to Isosulfan blue have a rate of about 1-3%.[57–59] Thus, the risks of allergic reactions to LUMISIGHT are mitigated in part because it will be administered in a healthcare setting by medical professionals that are already well-trained and equipped to manage allergic reactions and anaphylaxis.

8.8 Safety Conclusions

The safety profile of LUMISIGHT when injected at 1 mg/kg has been characterized in 726 patients: 703 patients with breast cancer and 23 patients with other cancers. All patients received a single dose of LUMISIGHT.

Results showed that 1 mg/kg IV dose of LUMISIGHT (N = 726 patients) was well tolerated. The principal safety risks associated with LUMISIGHT are anaphylaxis and hypersensitivity. To mitigate this risk, the proposed Prescribing Information includes instructions to obtain history of allergic and hypersensitivity reactions from each patient,

to only administer LUMISIGHT in a healthcare setting with emergency resuscitation equipment and trained personnel available; to monitor patients for 15 minutes after administration, and interrupt administration if a hypersensitivity reaction is suspected.

Overall results from clinical trials in patients with breast cancer and other solid tumors support the safe use of LUMISIGHT in breast cancer patients.

In summary:

- LUMISIGHT is well tolerated as evidenced by its safety profile characterized when administered as single dose of 1 mg/kg across multiple clinical studies that enrolled a total of 726 patients.
- There were no deaths.
- Related life-threatening AEs (0.1%), SAEs (0.6%), and AEs leading to discontinuation (1%) as well as unrelated life-threatening AEs (0.1%) and unrelated SAEs (0.4%), were reported infrequently.
- Most AEs are mild in severity.
- The expected AE of chromaturia is the most frequently reported AE, occurring in 85% of patients.
- Although LUMISIGHT does pose a risk of anaphylaxis, the frequency and severity of this risk is mitigated through the labeling of the product, post-injection monitoring, and administration in a pre-operative hospital setting that is prepared to immediately administer medication to treat and manage potential reactions.

9 POST-MARKETING PLAN

The FDA informed Lumicell on October 6, 2023 that the Agency anticipated that a post-marketing study will be required to assess the incidence of anaphylactic and other hypersensitivity effects. Lumicell agreed with this recommendation by the FDA to conduct an observational study to further assess the risk of anaphylaxis and hypersensitivity. The Sponsor plans to have further discussions with the FDA to finalize the study design, objectives, and sample size after the approval of LUMISIGHT's NDA.

10 BENEFIT-RISK CONCLUSIONS

The LUMISIGHT and the Lumicell DVS combination product has a positive benefit-risk profile. This imaging system, as an adjunct to SoC BCS, identified residual cancer that was left behind during the SoC BCS procedure, as well as converted patients from positive margins to final negative margins by excising LUM-guided shaves. All of this was achieved by removing tissue that did not appear to impact patient's perceived cosmetic outcomes. These benefits outweigh the manageable risk of potential hypersensitivity AEs in the pre-operative hospital setting.

10.1 Benefit-Risk Assessment

Results show that the LUM System enabled real-time assessment of the breast cancer lumpectomy cavity and facilitated removal of residual cancer left behind after SoC BCS. In Pivotal Study CL0007, the LUM System as an adjunct to SoC provided multiple benefits, including:

- Providing imaging results immediately available to the surgeon, requiring approximately 1 minute to scan the entire lumpectomy cavity, with all interventions adding less than 7 minutes to the operative procedure.
- Identifying residual cancer within 2-5 mm from the surface of the lumpectomy cavity, rather than on the surface of the excised lumpectomy specimen like standard margin assessment, frozen section, and other available tools. This avoids the inherent problem of specimen-based approaches, correlating the location of tumor on an excised deformable specimen surface with the location of residual tumor in the breast cavity.
- Allowing for repeat imaging of areas of concern during the initial SoC BCS to verify the removal of all positive signal areas.
- Guiding the removal of residual cancer remaining after SoC BCS in 27 of 357 (8%) patients. The residual cancer deposits excised included areas of low- and high-grade tumor ranging from 1 to 13 mm in size. Whether or not this residual disease that otherwise would have remained behind could account for recurrences following breast conserving surgery warrants further investigation.
- Converting 9 of 62 (14.5%) patients with SoC positive margins to final negative margins by excising LUM-guided shaves. In 8 of these 9 patients, a second surgery was avoided, reducing the patient and hospital burden of an additional surgery.

As for the risks of LUMISIGHT administration:

- Favorable safety profile and well-tolerated, with low frequency of non-chromaturia AEs and related SAEs (0.6% [4/726 patients]), and no device related AEs reported across the clinical study program.

- All related hypersensitivity events occurred in the pre-operative hospital setting and were managed by pre-op personnel well-trained in the identification and treatment of such allergic reactions.
- All patients fully recovered and proceeded on to SoC lumpectomy.
- To further mitigate risk of adverse reactions or device events, the Sponsor has proposed additional warnings and details in the Prescribing Information for LUMISIGHT including:
    - Clearly indicate the risk of "life-threatening anaphylaxis" in the Highlights section and the Warnings and Precautions section.
    - Advise healthcare providers that before LUMISIGHT administration, obtain history of allergy, hypersensitivity, or prior hypersensitivity reactions.
    - Indicate that patients with history of multiple food or drug allergies, or other hypersensitivities may be at an increased risk.
    - Specify to always administer LUMISIGHT in healthcare settings and have emergency resuscitation equipment and trained personnel available.
    - Instruct that if hypersensitivity reaction is suspected, interrupt injection.
    - Monitor patients for 15 minutes after injection.

Considering the benefits and risks identified in the Pivotal Study, the totality of the clinical benefits of the LUM System outweigh the potential safety risks, which can be well-managed in a pre-operative hospital setting and are clearly identified in the Prescribing Information.

Given the low complication rate, minimal added operative time and, most importantly, the discovery of additional cancer left behind after a lumpectomy, LUMISIGHT and the Lumicell DVS have the potential to be a critical adjunct to enhance standard practice for breast cancer patients. Hence, the benefit-risk assessment supports the proposed indication 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.

11 REFERENCES

1. SEER Cancer Stat Facts: Female Breast Cancer [Internet]. Available from: https://seer.cancer.gov/statfacts/html/breast.html

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73(1):17–48.

3. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999;340(19):1455–61.

4. Wazer DE, Schmidt-Ullrich RK, Ruthazer R, et al. Factors determining outcome for breast-conserving irradiation with margin-directed dose escalation to the tumor bed. Int J Radiat Oncol Biol Phys 1998;40(4):851–8.

5. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C. Pathologic findings from the national surgical adjuvant breast project (NSABP) protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). Cancer 1995;75(6):1310–9.

6. Breast Cancer Treatment | Cancer Trends Progress Report [Internet]. [cited 2023 Dec 26];Available from: https://progressreport.cancer.gov/treatment/breast_cancer

7. Havel L, Naik H, Ramirez L, Morrow M, Landercasper J. Impact of the SSO-ASTRO Margin Guideline on Rates of Re-excision After Lumpectomy for Breast Cancer: A Meta-analysis. Ann Surg Oncol 2019;26(5):1238–44.

8. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. N Engl J Med 2023;388(7):585–94.

9. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343. JCO 2013;31(19):2382–7.

10. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. Practical Radiation Oncology 2016;6(5):287–95.

11. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–106.

12. Sopik V, Lim D, Sun P, Narod SA. Prognosis after Local Recurrence in Patients with Early-Stage Breast Cancer Treated without Chemotherapy. Curr Oncol 2023;30(4):3829–44.

13. Dupont E, Tsangaris T, Garcia-Cantu C, et al. Resection of Cavity Shave Margins in Stage 0–III Breast Cancer Patients Undergoing Breast Conserving Surgery: A Prospective Multicenter Randomized Controlled Trial. Annals of Surgery 2021;273(5):876–81.

14. Bundred JR, Michael S, Stuart B, et al. Margin status and survival outcomes after breast cancer conservation surgery: prospectively registered systematic review and meta-analysis. BMJ 2022;378:e070346.

15. Tringale KR, Pang J, Nguyen QT. Image-guided surgery in cancer: A strategy to reduce incidence of positive surgical margins. Wiley Interdiscip Rev Syst Biol Med 2018;10(3):e1412.

16. Tang R, Coopey SB, Specht MC, et al. Lumpectomy specimen margins are not reliable in predicting residual disease in breast conserving surgery. Am J Surg 2015;210(1):93–8.

17. Schnabel F, Boolbol SK, Gittleman M, et al. A Randomized Prospective Study of Lumpectomy Margin Assessment with Use of MarginProbe in Patients with Nonpalpable Breast Malignancies. Ann Surg Oncol 2014;21(5):1589–95.

18. Ihrai T, Quaranta D, Fouche Y, et al. Intraoperative radiological margin assessment in breast-conserving surgery. Eur J Surg Oncol 2014;40(4):449–53.

19. Rabindran B, Corben AD. Wide-field optical coherence tomography for microstructural analysis of key tissue types: a proof-of-concept evaluation. Pathol Oncol Res 2023;29:1611167.

20. Carter D. Margins of “Lumpectomy” for breast cancer. Human Pathology 1986;17(4):330–2.

21. Fisher B, Anderson S, Bryant J, et al. Twenty-Year Follow-Up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy, and Lumpectomy Plus Irradiation For The Treatment of Invasive Breast Cancer. New England Journal of Medicine 2002;347(16):1233–41.

22. McCormick B, Winter KA, Woodward W, et al. Randomized Phase III Trial Evaluating Radiation Following Surgical Excision for Good-Risk Ductal Carcinoma In Situ: Long-Term Report From NRG Oncology/RTOG 9804. JCO 2021;39(32):3574–82.

23. Wapnir IL, Dignam JJ, Fisher B, et al. Long-Term Outcomes of Invasive Ipsilateral Breast Tumor Recurrences After Lumpectomy in NSABP B-17 and B-24 Randomized Clinical Trials for DCIS. JNCI Journal of the National Cancer Institute 2011;103(6):478–88.

24. Whitley MJ, Cardona DM, Lazarides AL, et al. A mouse-human phase 1 co-clinical trial of a protease-activated fluorescent probe for imaging cancer. Sci Transl Med 2016;8(320):320ra4.

25. Mustafa A, Elkhamisy F, Arghiani N, Pranjol MZI. Potential crosstalk between pericytes and cathepsins in the tumour microenvironment. Biomedicine & Pharmacotherapy 2023;164:114932.

26. Shivers S, Cox C, Leight G, et al. Final results of the department of defense multicenter breast lymphatic mapping trial.

27. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer. JCO 2014;32(14):1507–15.

28. Meattini I, Marrazzo L, Saieva C, et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020;38(35):4175–83.

29. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. The Lancet 2011;378(9804):1707–16.

30. Breast Cancer Facts & Figures [Internet]. [cited 2024 Jan 10];Available from: https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html

31. Lumpectomy (Breast Lump Removal) | Gleneagles Hospital [Internet]. GEH. [cited 2024 Jan 26];Available from: https://admin-gleneagles.parkwayhealth.local/tests-treatments/lumpectomy

32. Keum H, Park HY, Kang B, Jung JH, Kim WW, Lee J. Comparison of margin assessment between intraoperative digital and conventional specimen mammography in breast cancer: A preliminary study. Asian Journal of Surgery 2023;46(5):1931–6.

33. Figure 1. Marking resected cavity shave margins. [Internet]. ResearchGate. [cited 2024 Jan 26];Available from: https://www.researchgate.net/figure/Marking-resected-cavity-shave-margins_fig1_352913339

34. Ellis IO, carder p, hales s, et al. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer [Internet]. 2016;Available from: https://www.rcpath.org/static/7763be1c-d330-40e8-95d08f955752792a/G148_BreastDataset-hires-Jun16.pdf

35. Whelan TJ, Smith S, Parpia S, et al. Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. New England Journal of Medicine 2023;389(7):612–9.

36. Jagsi R, Griffith KA, Harris EE, et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol 2023;JCO2302270.

37. Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. The Lancet 2019;394(10215):2155–64.

38. Oncoplastic breast surgery - UpToDate [Internet]. [cited 2024 Jan 25];Available from: https://www.uptodate.com/contents/oncoplastic-breast-surgery

39. Macmillan RD, McCulley SJ. Oncoplastic Breast Surgery: What, When and for Whom? Curr Breast Cancer Rep 2016;8:112–7.

40. Citgez B, Yigit B, Bas S. Oncoplastic and Reconstructive Breast Surgery: A Comprehensive Review. Cureus 2022;14(1):e21763.

41. Leff DR, St John ER, Takats Z. Reducing the Margins of Error During Breast-Conserving Surgery: Disruptive Technologies or Traditional Disruptions? JAMA Surg 2017;152(6):517–8.

42. Smith BL, Hunt KK, Carr D, et al. Intraoperative Fluorescence Guidance for Breast Cancer Lumpectomy Surgery. NEJM Evidence [Internet] 2023 [cited 2023 Sep 15];2(7). Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2200333

43. Lanahan CR, Kelly BN, Gadd MA, et al. Performance of a novel protease-activated fluorescent imaging system for intraoperative detection of residual breast cancer during breast conserving surgery. Breast Cancer Res Treat 2021;187(1):145–53.

44. Smith BL, Gadd MA, Lanahan CR, et al. Real-time, intraoperative detection of residual breast cancer in lumpectomy cavity walls using a novel cathepsin-activated fluorescent imaging system. Breast Cancer Res Treat 2018;171(2):413–20.

45. Smith BL, Lanahan CR, Specht MC, et al. Feasibility Study of a Novel Protease-Activated Fluorescent Imaging System for Real-Time, Intraoperative Detection of Residual Breast Cancer in Breast Conserving Surgery. Ann Surg Oncol [Internet] 2020 [cited 2020 Feb 7];Available from: https://doi.org/10.1245/s10434-019-08158-1

46. Hwang ES, Beitsch P, Blumencranz P, et al. Clinical Impact of Intraoperative Margin Assessment in Breast-Conserving Surgery With a Novel Pegulicianine Fluorescence–Guided System: A Nonrandomized Controlled Trial. JAMA Surg [Internet] 2022 [cited 2022 May 31];Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2792167

47. Smith BL, Hunt KK, Carr D, et al. Intraoperative Fluorescence Guidance for Breast Cancer Lumpectomy Surgery. NEJM Evidence 2023;2(7):EVIDoa2200333.

48. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2018 [Internet]. SEER. [cited 2022 Nov 21];Available from: https://seer.cancer.gov/csr/1975_2018/index.html

49. Yadav S, Karam D, Bin Riaz I, et al. Male breast cancer in the United States: Treatment patterns and prognostic factors in the 21st century. Cancer 2020;126(1):26–36.

50. Chagpar AB, Killelea BK, Tsangaris TN, et al. A Randomized, Controlled Trial of Cavity Shave Margins in Breast Cancer. New England Journal of Medicine 2015;373(6):503–10.

51. Chagpar AB, McMasters KM, Saul J, et al. Body mass index influences palpability but not stage of breast cancer at diagnosis. Am Surg 2007;73(6):555–60; discussion 560.

52. Invasive Breast Cancer (IDC/ILC) [Internet]. [cited 2024 Jan 26];Available from: https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/invasive-breast-cancer.html

53. Swanick CW, Lei X, Xu Y, et al. Long-term Patient-Reported Outcomes in Older Breast Cancer Survivors: A Population-Based Survey Study. Int J Radiat Oncol Biol Phys 2018;100(4):882–90.

54. Nguyen TH, Han H-R, Kim MT, Chan KS. An introduction to item response theory for patient-reported outcome measurement. Patient 2014;7(1):23–35.

55. Wang X, Piantadosi S, Le-Rademacher J, Mandrekar SJ. Statistical Considerations for Subgroup Analyses. J Thorac Oncol 2021;16(3):375–80.

56. Kuhlen JL, Camargo CA, Balekian DS, et al. Antibiotics Are the Most Commonly Identified Cause of Perioperative Hypersensitivity Reactions. J Allergy Clin Immunol Pract 2016;4(4):697–704.

57. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am J Surg 2001;182(4):393–8.

58. Laurie SA, Khan DA, Gruchalla RS, Peters G. Anaphylaxis to isosulfan blue. Ann Allergy Asthma Immunol 2002;88(1):64–6.

59. Raut CP, Hunt KK, Akins JS, et al. Incidence of anaphylactoid reactions to isosulfan blue dye during breast carcinoma lymphatic mapping in patients treated with preoperative prophylaxis: results of a surgical prospective clinical practice protocol. Cancer 2005;104(4):692–9.

60. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

61. Welcome to MedDRA | MedDRA [Internet]. [cited 2024 Jan 28];Available from: https://www.meddra.org/

62. Common Terminology Criteria for Adverse Events (CTCAE) [Internet]. 2017;Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

63. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. Journal of Allergy and Clinical Immunology 2022;150(6):1333–93.

12 APPENDICES

12.1 Pivotal Study CL0007 Schedule of Events

Table 27: Schedule of Events

	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		
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			

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 are optional for enrollment. The Baseline evaluation can be completed by the patient at any time prior to the lumpectomy procedure. A validated survey tool, the Breast-Q, will be used to collect the majority of the PROMs.
[e.] If patient is randomized into the Device Arm.

12.2 Pivotal Study CL0007 Inclusion Criteria

Patients must meet the following criteria on screening examination to be eligible to participate in the study.

1. Patients must have histologically or cytologically confirmed primary invasive breast cancer, DCIS, or primary invasive breast cancer with a DCIS component. The methods for obtaining the histological samples can include core needle biopsies or fine needle biopsies. Patients who had diagnostic open surgical biopsies are excluded from participation.
2. 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 are excluded from this study.
3. Patients must be scheduled for a lumpectomy for a breast malignancy.
4. Patients must be able and willing to follow study procedures and instructions.
5. Patients must have received and signed an ICF.
6. Patients must have no uncontrolled serious medical problems except for the diagnosis of breast cancer, as per the exclusion criteria in Appendix 12.3.
7. Patients must have 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.
8. Patients with ECOG performance status of 0 or 1.

Note: Patients with a history of multiple drug allergies, atopic patients, and patients with atopic syndrome are eligible for the study but should be pre-medicated according to institution standards prior to injection with the LUMISIGHT imaging agent.

12.2.1 Inclusion of Women, Minorities and Other Underrepresented Populations

As this study is to test the efficacy of an intraoperative imaging technology in female breast cancer patients, all of the patients will be women. Males with breast cancer (<1% of breast cancer patients) usually undergo mastectomy procedures and only rarely have lumpectomies, and thus are not eligible for this study.

12.3 Pivotal Study CL0007 Exclusion Criteria

Patients who exhibit any of the following conditions at screening will not be eligible for admission into the study.

1. Patients who have been diagnosed with bilateral breast cancer and are undergoing a bilateral resection procedure.
2. Patients who are 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.
3. Patients who are sexually active and not willing/able to use 2 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.
4. Patients who have taken an investigational drug within 30 days of enrollment.
5. Patients who will have 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.
6. Patients who have not recovered from AEs due to other pharmaceutical or diagnostic agents.
7. Patients with uncontrolled hypertension defined as persistent systolic blood pressure > 180 mm Hg, or diastolic blood pressure > 110 mm Hg; those patients with known HTN should be stable with controlled HTN while under pharmaceutical therapy.
8. History of allergic reaction to polyethylene glycol (PEG).
9. History of allergic reaction to any oral or IV contrast agents.
10. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, COPD or asthma requiring hospitalization within the past 12 months, or psychiatric illness/social situations that would limit compliance with study requirements.
11. HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with LUMISIGHT.
12. Any patient for whom the investigator feels participation is not in the best interest of the patient.

13. Patients undergoing a second lumpectomy procedure because of positive margins in a previous surgery prior to entering this study.
14. Patients with post-biopsy hematomas greater or equal to 2 cm that are visible on physical exam or detected during pre-operative observations.
15. Patients with prior ipsilateral breast cancer surgeries, mastectomies, breast reconstructions or implants.
16. Patients with prior ipsilateral reduction mammoplasties (breast reductions) performed less than 2 years prior to enrollment to this study.
17. 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.
18. Patients undergoing BCS whose resected specimen (main lump, shaves, or any other resected tissue) will be evaluated with frozen section after the LUM-guided removal of shaves.

Note: It is unknown whether neoadjuvant radiation therapy affects the tumor environment and its response to LUMISIGHT; thus, patients previously treated with neoadjuvant therapy should be excluded per Exclusion Criteria 17.

12.4 Pivotal Study CL0007 Secondary Endpoints

12.4.1 Efficacy Secondary Endpoints Not Reported in Section 7.1.8

Secondary Endpoints	Results	Clinical Relevance
Percent of patients with positive margins after SoC BCS with LUM-positive signal corresponding all positive margin orientations n (%) (patient-level)	10/62 16.1%; 95% CI [8.0%, 27.7%]	In 62 patients with positive margins after the SoC procedure, 10 patients had positive Lumicell signal matching all positive margin orientations. However, 9 were concerted to final negative margins by excising LUM-guided shaves are presented in Section 7.1.8.1.
Percent of patients with negative SoC margins with tumor found in LUM-guided shaves (patient-level)	19/295 6.4%; 95% CI [3.9%, 9.9%]	These 19 patients are presented in Section 7.1.7.1. Overall impact of patients with negative margins in which a LUM-guided shave removed residual cancer missed during the initial surgery.
Percent of patients with negative SoC margins with tumor found in LUM-guided shaves among all patients (patient-level)	19/357 5.3%; 95% CI [3.2%, 8.2%]	

Secondary Endpoints	Results	Clinical Relevance
Percent of second surgeries as a result of a final positive margin status following SoC (control arm) and Lumicell imaging procedure (patient-level)	Control arm: 7/35 20.0%; 95% CI [8.4%,36.9%] After Lumicell: 47/357 13.2%; 95% CI [9.8%,17.1%]	Note that not all patients with positive margins were recommended to have a second surgery.
Rate of cancer found in second surgeries (patient-level)	21/54 38.9%; 95% CI [25.9%, 53.1%]	From the 54 patients that had second surgeries, pathology found cancer in 21 of them for a rate of ~39%.
Number of second surgeries for each patient (patient-level)	48 patients had 1 follow-up surgery, 4 patients had 2 follow-up surgeries, and 2 patients had 3 follow-up surgeries	Most patients with positive margins had just 1 follow-up surgery, however there were 2 patients that required 3 follow-up surgeries to get negative margins.
Number of images per patient from the cavity after SoC and first round of LUM-guided shaves (patient-level)	After SoC: Mean (SD) = 5.91 (1.0) Median (Min, Max) = 6.00 (1.0,14.0)	After SoC BCS, on average, all 6 orientations of the lumpectomy cavity were imaged.
	After 1 round of LUM-guided shaves: Mean (SD) = 1.61 (0.8) Median (Min, Max) = 1.00 (1.0,5.0)	
Secondary analysis of sensitivity and specificity including non-guided imaging before removal of SoC shaves (tissue-level)	Sensitivity: 78/161 48.3%; 95% CI [39.8%, 56.9%]	This result is consistent with the sensitivity and specificity reported in the primary endpoints.
	Specificity: 2284/2805 83.1%; 95% CI [81%, 85%]	
Number of device issues and malfunctions and their impact to data capture	Out of 202 potential issues recorded, 12 device issues had impact to data capture. Five of these led to discontinuation of the imaging procedures in 4 patients (1 patient had 2 device issues), which include the following: • A software issue in which the camera lost connection with computer • Probe size was too large to fit into the surgical incision	Lumicell collected all potential device issues as part of the continuous evaluation of a new investigational device; all potential issues were evaluated for potential impact to patient or user safety, and data capture and integrity. All potential device issues, except the 5 mentioned, allowed completion of the Lumicell imaging procedures. A full list of the findings will be included in the pivotal trial CSR.

Secondary Endpoints	Results	Clinical Relevance
	• (patient with 2 device issues) Device failed initialization procedure, and laptop connected to WIFI, tried to update operating system for too long • Tegaderm used in securing sterile barrier unpeeled The remaining 7 device issues allowed data collection from the imaging procedure that was included in the efficacy analysis.	No AEs caused by or related to the use of the device were reported.
Exploratory data on tissue types found in LUM-guided shaves	When no tumor is found in Lumicell-guided shaves, abnormal tissues were confirmed in more than 64% of the shaves, including usual ductal hyperplasia, atypical ductal hyperplasia, lobular carcinoma in situ (LCIS) and inflammation, among others.	Provides information to surgeons on what can be found in LUM-guided shaves without tumor.
Analysis of tissue-level sensitivity and specificity for the SoC procedure based on the outermost SoC resected surface (tissue-level)	Sensitivity: 24/51 47%; 95% CI [34%, 60%]	Sensitivity and specificity of margin pathology in predicting cancer in the cavity based on the outermost SoC tissue margin only when ground truth is available (LUM-guided shave or tissue from a second surgery)
	Specificity: 233/276 84%; 95% CI [80%, 88%]	

AE: Adverse event; BCS: Breast conserving surgery; CI: Confidence interval; CSR: Clinical study report; LCIS: lobular carcinoma in situ; SAP: Statistical analysis plan; SoC: Standard of care

12.5 Representativeness of Study Participants in the Pivotal Study to the Broader Breast Cancer Population undergoing BCS

Representativeness of Study Participants	
Disease under investigation	Histologically or cytologically confirmed primary invasive breast cancer, DCIS, or primary invasive breast cancer with a DCIS component

Representativeness of Study Participants	
Special considerations related to:	
Sex and gender	Breast cancer is the most common malignancy among women worldwide[60] and is the most common cancer in women in the United States, after non-melanoma skin cancers. Breast cancer in men is rare, accounting for less than 1% of all breast cancer cases in the United States[48]. Therefore, only women were enrolled into this study.
Age	The median age of breast cancer diagnosis in the population represented by Surveillance Epidemiology and End Results (SEER) data is 63 years[48], similar to the median age of patients in this Pivotal Study (62 to 64 years of age across the study population groups.
Race or ethnic group	Non-Hispanic white women and non-Hispanic Black women have the highest incidence of breast cancer overall. Hispanic women have the lowest incidence.[1] Most of the participants in this trial were non-Hispanic white women.
Geography	Rates of breast cancer incidence vary across the U.S.[30] This study enrolled participants at 14 institutions across 12 different states.
Other considerations	The median tumor size was 1.5 cm in the safety and efficacy study populations (i.e., largest dimension of tumor in the main lumpectomy specimen) and 1.9 cm in the Control Population. These data were comparable to published literature on tumor size in similar populations.[51] The tumor histology data showed approximately 70.0% of patients across the population groups had tumors of IDC or DCIS origin, which is comparable to data in published literature that showed IDCs contributed to approximately 80.0% of the newly diagnosed population.[52]
Overall representativeness of this trial	The participants in this trial demonstrated the expected sex and age distribution. The proportion of Black women who participated was small (6%). The tumor characteristics data of the participants in this study were representative of the US population of newly diagnosed patients with breast cancer. The distribution of age, sex, race, ethnicity, and the calculated BMI were found to be very similar between the study populations.

BMI: Body mass index; DCIS: Ductal carcinoma in situ; IDC: Invasive ductal carcinoma

12.6 Adverse Event Identification and Classification

AEs were identified through systemic assessment. Blood test values were collected at baseline and post-operative (median 13 days after lumpectomy). Clinically significant changes in blood values were reported as AEs. Clinical trial personnel were present during LUMISIGHT injections and required to document if a potential hypersensitivity event occurred. Participant medical records were reviewed by both clinical site personnel and by Lumicell monitoring personnel to identify any AEs that were reported while the patient was on-study. Clinical personnel interviewed participants during the follow-up visit to identify and report AEs. An independent Medical Monitor reviewed all the CRFs for AEs (including the reported AEs, medical history, concomitant medications, and other relevant information reported in the CRF).

The Medical Dictionary for Regulatory Activities (MedDRA)[61] is standardized medical terminology to facilitate sharing of regulatory information for medical products used by humans. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed and governs MedDRA. MedDRA version 22.1 was used to code AEs in Lumicell's trials. Reported AEs were entered in the EDC system. A Certified MedDRA Coder (CMC) coded each reported AE using the MedDRA module within the EDC. The independent Medical Monitor reviewed all coded terms prior to database lock.

The CTCAE v. 5.0[62] was used to classify AEs during Lumicell's trials. Version 5.0 was published on November 27, 2017 and is the current version. This NCI CTCAE is a descriptive terminology which is utilized for AE reporting. A grading (severity) scale is provided for each AE term. The AE terms are each a unique representation of a specific event used for medical documentation and scientific analysis. Each CTCAE term is a MedDRA Lowest Level Term (LLT), also known as a Preferred Term (PT). The CTCAE criteria are designed to ensure that AEs are reported consistently and accurately across different trials and institutions.

As described above, severity was determined according to the CTCAE. Seriousness was graded according to 21CF312. Therefore, an event may be classified as severe per CTCAE, but not meet the definition of Serious.

12.7 Serious Adverse Events Related to LUMISIGHT

Table 28: Summary of Serious Adverse Events Related to LUMISIGHT

Study Identifier	CL0006	CL0007	CL0007	CL0008
Patient identifier	1	2	3	4
Relevant baseline information	Reported hives in response to oral and IV iodine contrast agent.	None	None	None
Reported adverse event term	anaphylaxis (includes hypotension and cyanosis)	Allergic reaction	Anaphylaxis reaction	Anaphylaxis
Dictionary-derived AE term	Anaphylactic reaction	Hypersensitivity	Anaphylactic reaction	Anaphylactic reaction
Date of LUMISIGHT injection	(b) (6)	25MAR2021	(b) (6)	27MAY2022
AE time of onset relative to injection	During injection, 1.5-2 minutes after start of administration	During injection, 2 minutes after start of administration	During injection, 1.5 minutes after start of administration	Several minutes after completion of injection, then 3 hours after injection and wire localization
Symptoms	Shortness of breath, chest tightness, diaphoretic, nausea, apneic and cyanotic for a brief period	Nausea and vomiting, profuse erythema, hypotension	shortness of breath, tingling in tongue, hands and feet, swollen lip, nausea, and vomiting	Hypotension, itchy hands and feet, lip numbness
Treatment	Oxygen via bag-mask, IV Epinephrine, IV solumedrol, IV Benadryl	IV Zofran, IV Benadryl	IV Benadryl, hydrocortisone, Zofran, Pepcid	IV fluids, then ephedrine after wire localization
Recovery	Patient transferred to ICU where she recovered and was discharged next day	25 minutes after onset	20-30 minutes after onset	30 minutes after onset
Relatedness (reported in trial)	Definitely Related	Definitely Related	Definitely Related	Possibly Related

Study Identifier	CL0006	CL0007	CL0007	CL0008
AE severity (reported in trial)	Life Threatening	Severe	Severe	Severe
Date of lumpectomy	(b) (6)	26MAR2021	(b) (6)	27MAY2022
Blood sample test results for total complement, histamine and tryptase	Not available, blood sample not collected	Histamine above normal range Tryptase slightly over normal range Total complement within normal range	Histamine above normal range Tryptase and total complement within normal range	Total complement, tryptase and histamine within normal ranges
Additional considerations from post-hoc review	• Confirmed assessment of anaphylaxis • Etiology could have been cefazolin vs LUMISIGHT	• Confirmed assessment of anaphylaxis • With exception of diffuse erythema, remaining symptoms could be suggestive of vasovagal event, however, her elevated tryptase, histamine, and initially a low complement suggest immune-mediated reaction. There is no baseline tryptase to compare this to, but in the setting of the clinical findings its relevance cannot be ignored. A baseline tryptase, if elevated, could affect this conclusion.	• Patient's symptoms were mostly subjective, except for lip angioedema which is reported as the patient felt lip swelling. Although this is considered an objective symptom, there is no objective documentation of this finding, leaving it unclear if any objective symptoms were present. • Dyspnea reported, but no documentation of tachypnea, hypoxia, wheezing or other symptoms available. • Patient improved quickly with several medications with positive lab results. • Event may be anxiety reaction, but hypersensitivity cannot be excluded due to dyspnea and angioedema reported.	• Vasovagal reaction is in the differential • Symptoms resolved with fluids alone, suggesting against diagnosis of allergic hypersensitivity

AE: Adverse event; IV: Intravenous; Y: Yes

12.8 Allergists Panel Review of Allergic Reactions

12.8.1 Panel Evaluations for SAE from Patients 3 and 4

Patient 3:

Reaction phenotype most suggestive of a nonimmune-mediated AE, likely psychosomatic symptoms or acute stress response. As psychosomatic symptoms and acute stress response are diagnoses of exclusion, the final review focused on supportive evidence against diagnosis of immune-mediated drug reaction, which includes anaphylaxis. The patient reported immediate symptoms that were all subjective without observed physical exam findings to corroborate swelling, nor to suggest episode of emesis. Additionally, no increased work of breathing, cutaneous findings, or evidence of hypotension or hypoxia were noted during this episode, all suggesting against immediate allergic event. Hospital records indicate resolution of symptoms within 20-30 minutes of receiving treatment, including resolution of subjective lip swelling. Even though the patient received medication therapy intravenously, Benadryl and hydrocortisone would not be expected to have reached peak efficacy by that time (peak onset of action is observed at 2 and 1 hour, respectively), suggesting that treatment was not fully required for symptomatic resolution. This also suggests that the reactions are not immune mediated, which would not be expected to completely resolve in such a short (~20 minutes) timeframe. Additionally, the patient did not have a significant elevation in tryptase, which is the most specific biomarker indicative of anaphylaxis. Of note, this patient did have elevation in histamine with maintained (though down trending) elevated histamine on repeat lab draw at 1-hour post-reaction; although this could be suggestive of possible mast cell degranulation association with immune mediated response, histamine as a biomarker is non-specific and therefore not indicative or diagnostic of immune-mediated reaction. This event was termed as a possible allergic reaction and considered to be moderate (not severe as reported in the trial). The reaction would be not be classified as anaphylaxis according to the Anaphylaxis Practice Parameters Severity Grading System for acute allergic reactions.[63]

Patient 4:

Determined to not have been an anaphylactic reaction, but a vasovagal event that was moderate in nature. For this patient, although vasovagal syncope is the most likely diagnosis, allergic reaction is unlikely to be the etiology of the symptoms. However, the gold standard of disproving allergic reactions via supervised challenge to the potential inciting medication, which had not been performed, and thus allergy cannot be definitively ruled out. In the unlikely scenario that this was an allergic reaction, based on the objective symptom of hypotension, this reaction would be consistent with a moderate risk cardiovascular event and a Grade 3 AE, regardless of not meeting criteria for anaphylaxis (based on Anaphylaxis Practice Parameters Severity Grading system for acute allergic reactions and USDAR severity scoring, respectively).

12.8.2 Panel's Hypothesis on Possible MOA for Allergic Reactions

Based on review of the information available by the allergists panel, it remains possible that the 4 SAEs were related to the LUMISIGHT injection. However, as in most allergic reactions of unknown origin, the true etiology of the reported SAEs may have been confounded. Even with the inability to determine the precise etiology of the hypersensitivity events reported in these clinical studies, the panel strongly suspects that these reactions involved mast cell activation. Mast cells are essentially the only cell in the body that produces the chemical tryptase and is the primary producer of histamine. Two of 3 patients that experienced the SAEs had elevated tryptase, 1 patient did not have labs drawn after the reaction, and 1 did not have elevated tryptase (the event that is determined to be more likely vasovagal versus allergy). There are not many known mechanisms by which drugs could cause mast cell degranulation in the absence of drug specific IgE, except though direct stimulation a specific receptor on the mast cell. It is hypothesized that LUMISGHT molecule itself is able to directly stimulate this mast cell receptor and induce activation and degranulation of the mast cells, without needing any antibody.

12.8.3 Panel Review of Non-Serious Hypersensitivity Cases

Table 29: Allergist Review of Non-Serious Hypersensitivity Cases

Allergist review	Data Reported in Clinical Trial			
	Event term	AE Severity	Histamine results (immediately post-reaction)	Histamine results (30-minute post-reaction)
Moderate reaction developed 2 days after injection, unable to determine causality due to confounding med exposures, unclear, remains possible that delayed urticaria was related to LUMISIGHT	Urticaria	Moderate	N/A	N/A
Moderate reaction, possible allergic reaction, probably related, no tryptase elevation, quick resolution suggestive against immune-mediated allergy	Hypersensitivity	Moderate	13	43
Moderate event, anxiety attack (hyperventilation), possibly related, immediate resolution of symptoms with Versed and 12.5 mg Benadryl, fast resolution is inconsistent with immune-mediated reaction, which would require a larger dose of Benadryl, however, histamine	Hypersensitivity	Severe	22	12

Allergist review	Data Reported in Clinical Trial			
	Event term	AE Severity	Histamine results (immediately post-reaction)	Histamine results (30-minute post-reaction)
elevated so cannot rule out allergic reaction.				
Moderate reaction, possible allergic reaction, probably related, vitals remained normal, symptoms experienced within 10 minutes of receiving LUM, timeline could be c/w immediate immune-mediated reaction likely related, symptoms are overall mild in nature (with exception of CTCAE grading system).	Hypersensitivity	Moderate	N/A	17
Mild reaction, many confounding meds, unclear if symptoms attributed to LUMISIGHT.	Pruritus	Mild	N/A	N/A

AE: Adverse event; N/A: Not applicable

12.9 Listing of Academic/Non-Academic Clinical Sites That Participated in Pivotal Breast Cancer Study

Table 30: Pivotal Study Clinical Trial Sites – Academic and Non-Academic

Site	Academic (A) or Non-Academic (N)
Massachusetts General Hospital	A
Duke University Hospital	A
Stanford University Medical Center	A
MD Anderson	A
Penn State - Hershey	A
Baptist MD Anderson Cancer Center	A
Cleveland Clinic	A
Mitchell Cancer Institute - University of South Alabama	A
Beaumont Hospital, Royal Oak	A
Moffitt Cancer Center	A
CHI Franciscan Research Center	N
Novant Health Clinical Research	N

Site	Academic (A) or Non-Academic (N)
The Comprehensive Breast Care Center of Tampa Bay (Baycare Medical Group)	N
Ironwood Cancer and Research Center (Honor Health)	N

A: Academic; N: Non-Academic

12.10 Severe Adverse Events

Table 31: Severe Adverse Events

Patient	Preferred Term	Start Date	End Date	Serious Event	Related to LUMISIGHT	Date of LUMISIGHT Injection	Tumor Type
1	Presyncope	11NOV2020	11NOV2020	N	Not Related	11NOV2020	Pancreatic Undergoing Neoadjuvant Therapy
2	Alanine aminotransferase increased	29OCT2018	09NOV2018	N	Related	23OCT2018	Breast
3	Acute myocardial infarction	26JAN2021	26JAN2021	N	Not Related	26JAN2021	Breast
3	Hypotension	26JAN2021	26JAN2021	N	Not Related	26JAN2021	Breast
4	Hypersensitivity	25MAR2021	25MAR2021	Y	Related	25MAR2021	Breast
5	Breast pain	14JAN2020	04FEB2020	N	Not Related	14JAN2020	Breast
6	Chronic kidney disease	05APR2021	09APR2021	N	Not Related	19MAR2021	Breast
6	Acute kidney injury	09APR2021	15APR2021	Y	Not Related	19MAR2021	Breast
6	Breast cellulitis	09APR2021	29APR2021	Y	Not Related	19MAR2021	Breast
7	Vascular pseudoaneurysm	02OCT2020	02OCT2020	Y	Not Related	01OCT2020	Breast
8	Back pain	17FEB2021	17FEB2021	N	Not Related	17FEB2021	Breast

Patient	Preferred Term	Start Date	End Date	Serious Event	Related to LUMISIGHT	Date of LUMISIGHT Injection	Tumor Type
9	Hypersensitivity	10FEB2021	10FEB2021	N	Related	10FEB2021	Breast
10	Anaphylactic reaction	25AUG2021	25AUG2021	Y	Related	25AUG2021	Breast
11	Anaphylactic reaction	27MAY2022	27MAY2022	Y	Related	27MAY2022	Breast

N: No; Y: Yes

12.11 PROM Questionnaire

For each question, the patient responds using a 4-point scale ranging from 1 (Very Dissatisfied) to 4 (Very Satisfied).

Table 32: PROM Questionnaire Before and After Surgery

	PROM Survey - Pre-Surgery Satisfaction	PROM Survey - Post-Surgery Satisfaction
Questions in both pre- and post-surgery questionnaires	a. How you look in the mirror clothed?	a. How you look in the mirror clothed?
	c. Being able to wear clothing that is more fitted?	d. Being able to wear clothing that is more fitted?
	d. How you look in the mirror unclothed?	k. How you look in the mirror unclothed?
Questions only in the pre-surgery questionnaires	b. How comfortably your bras fit?	
Questions only in the post-surgery questionnaires		b. The shape of your lumpectomy breast when you are wearing a bra?
		c. How normal you feel in your clothes?
		e. How your lumpectomy breast sits/hangs?
		f. How smoothly shaped your lumpectomy breast looks?
		g. The contour (outline) of your lumpectomy breast?
		h. How equal in size your breasts are to each other?
		i. How normal your lumpectomy breast looks?
		j. How much your breasts look the same?

PROM: Patient-reported outcomes measure