FDA Briefing Document

NDA 214511

Drug name: pegulicianine

Applicant: Lumicell, Inc.

Medical Imaging Drug Advisory Committee Meeting

March 5, 2024

Division of Imaging and Radiation Medicine/Office of Specialty Medicine

DISCLAIMER STATEMENT

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Glossary

AC	Advisory Committee
AE	adverse event
BCS	breast-conserving surgery
CDER	Center for Drug Evaluation and Research
CI	confidence interval
DCIS	ductal carcinoma in situ
DVS	Direct Visualization System
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FMQ	FDA MedDRA query
FN	false negative
FP	false positive
IRR	infusion-related reaction
mITT	modified intent- to- treat
PEG	polyethylene glycol
REMS	risk evaluation and mitigation strategy
SoC	standard of care
TN	true negative
TP	true positive

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee (AC) meeting to discuss the persuasiveness of the evidence of performance of pegulicianine (proposed tradename LUMISIGHT) and to obtain advice on risk mitigation for hypersensitivity reactions, including anaphylaxis, to inform the benefit-risk assessment for LUMISIGHT.

1.2 Context for Issues to be Discussed at the AC

Breast cancer is a life threatening and irreversibly debilitating disease and is the most common cancer in women in the United States. Therapy for breast cancer without known metastasis typically consists of surgical resection of the breast tumor and sampling or removal of axillary lymph nodes, often followed by postoperative radiation. Incomplete resection of tumor is one of the primary prognostic factors for ipsilateral breast tumor recurrence. Currently, no FDA-approved intraoperative technology is available that directly examines the lumpectomy cavity for residual cancer after the main specimen is removed in breast-conserving surgery (BCS).

LUMISIGHT and the Lumicell Direct Visualization System (DVS) are the drug and device constituents, respectively, of a combination product intended to assist in the detection of cancerous tissue in the resection cavity following removal of the primary specimen during lumpectomy surgery.

1.3 Brief Description of Issues for Discussion at the AC

Data provided by the Applicant to demonstrate effectiveness of LUMISIGHT are derived from two studies, CL0007, considered to be adequate and well-controlled, and CL0006, submitted as confirmatory evidence. CL0007 was a prospective, two-arm, randomized, blinded study that enrolled adult females with primary invasive breast cancer or ductal carcinoma in situ (DCIS) who were scheduled for lumpectomy. All enrolled patients received 1 mg/kg LUMISIGHT intravenously 2 to 6 hours prior to the scheduled surgery, regardless of randomization to the device arm or control arm (10:1). After completing BCS according to local standard of care (SoC), randomization was revealed to the surgeon. Patients in the device arm had imaging of the resection cavity with the Lumicell DVS and additional resection of LUMISIGHT-positive tissues, while patients in the control arm had no imaging or further resection. Histopathology results from resected tissue (both SoC and LUMISIGHT driven) served as the reference standard.

The co-primary efficacy endpoints were patient-level removal of residual cancer and tissue-level sensitivity and specificity. Removal of residual cancer was defined as the proportion of patients who had cancer in at least one therapeutic shave (LUMISIGHT-directed shave) among all patients in the modified intent-to-treat (mITT) population and was reported as 27 of 357 patients (7.6%; 95% confidence interval [CI]: 5.0%, 10.8%). The lower bound of the 95% CI exceeded the performance goal of 3%. Tissue-level sensitivity was 49.1% (34/69; 95% CI: 36.4%, 61.9%) and tissue-level specificity was 86.5% (1,940/2,277; 95% CI: 84.5%, 88.3%). Relative to the lower bounds of the 95% CIs, sensitivity did not meet its performance goal of 40% while specificity exceeded its performance goal of 60%. However, the Clinical and Statistical review teams consider the combined tissue-level sensitivity and specificity as demonstrating adequate diagnostic performance for imaging cancer in the lumpectomy cavity.

Cancer-related outcome measures were not assessed in the LUMISIGHT development program and data are not presented to support a benefit of removal of residual cancer on patient survival or ipsilateral breast tumor recurrence. However, patients who had positive margins after SoC surgery and converted to negative margins after LUMISIGHT-guided surgery would have a clear benefit of avoiding a second surgery to address positive margins. Among the 357 patients in the mITT population, 62 (17%) had positive margins after the SoC lumpectomy and SoC shaves, i.e., before LUMISIGHT-guided intervention. In 10 of these 62 patients (16.1%; 95% CI: 7%, 25.3%), LUMISIGHT fluorescence was found in the cavity at all orientations with positive margins. Nine of these patients (14.5% of patients with positive margins after SoC surgery [95% CI: 5.7%, 23.3%] and 2.5% of the mITT population [95% CI: 0.9%, 4.1%]) converted to negative margins after LUMISIGHT-guided resections. However, 8 of the 9 patients who converted from positive margins after SoC surgery to negative margins after LUMISIGHT-guided shaves did not have cancer in the LUMISIGHT-guided shaves.

The primary safety analysis population included 726 patients with cancer, predominantly breast cancer, who received an intended dose of 1 mg/kg LUMISIGHT. The overall rate of hypersensitivity was 4.8% (35/726; 95% CI:[1] 3.4%, 6.6%) and was composed of anaphylactic reactions at 0.6% (4/726; 95% CI: 0.2%, 1.4%) and other hypersensitivity reactions at 4.3% (31/726; 95% CI: 2.9%, 6.0%). Hypersensitivity reactions assessed as related by the study investigator occurred at a rate of 1.4% (10/726; 95% CI: 0.7%, 2.5%), and included all patients with anaphylactic reactions.

FDA has considered multiple strategies to mitigate risk and assess and further characterize the risk of anaphylaxis and serious hypersensitivity reactions for LUMISIGHT. Because LUMISIGHT is intended to be administered to patients 2 to 6 hours before intraoperative imaging, patients will be in a preoperative setting where it is expected that trained personnel, medications, and equipment necessary for management of serious hypersensitivity reactions are immediately available. A key risk mitigation step involves warning language in the drug labeling that reinforces the need to monitor patients for hypersensitivity reactions and to have appropriate personnel, medications, and equipment available. A boxed warning can further emphasize the risk and the need to monitor patients. Other potential risk mitigation and assessment measures include communicating the need for providers to evaluate patients for history of serious hypersensitivity to polyethylene glycol (PEG) or contrast media, requiring a post-marketing safety study to further characterize anaphylaxis and other hypersensitivity reactions, enhanced pharmacovigilance, restricting the indicated population to those with higher risk of having positive margins after standard of care lumpectomy, and a risk evaluation and mitigation strategy (REMS)[2].

1.4 Draft Points for Consideration

- Discuss whether the observed performance of LUMISIGHT for patient-level detection of residual cancer, tissue-level sensitivity, and tissue-level specificity provide sufficient evidence of effectiveness.
- Discuss the risk of serious hypersensitivity reactions associated with LUMISIGHT and the adequacy of risk mitigation and assessment strategies under consideration.
- Do the benefits of LUMISIGHT outweigh its risks?

[1] Exact confidence intervals are used when describing rates of adverse events.
[2] A REMS is a required risk management plan that uses risk minimization strategies beyond labeling.

- If yes, describe the clinically meaningful benefit and the risk mitigation measures that are recommended.
- If no, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment of LUMISIGHT.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Breast cancer is a life threatening and irreversibly debilitating disease and is the most common cancer in women in the United States. In 2020, 239,612 women were diagnosed with breast cancer in the United States, and this number may underestimate the true incidence due to the impact of the coronavirus disease 2019 pandemic (U.S. Cancer Statistics Working Group 2023). Breast cancer survival varies substantially by stage at diagnosis. The 5-year relative survival for patients diagnosed during 2012–2018 was >99% for stage I disease, 93% for stage II, 75% for stage III, and 29% for stage IV (American Cancer Society 2019).

Local treatment modalities are a critical component of therapy for breast cancer without known metastasis. Such therapy typically consists of surgical resection of the breast tumor and sampling or removal of axillary lymph nodes, often followed by postoperative radiation. Systemic chemotherapy (neoadjuvant, adjuvant, or both) and adjuvant endocrine therapy are variably employed depending on anatomic stage, tumor histology, receptor status, and other factors.

Most women diagnosed with early-stage breast cancer have the option of receiving either mastectomy or breast conserving surgery (BCS) plus adjuvant radiotherapy, as randomized clinical trials have reported equivalent survival outcomes with these therapeutic approaches (Fisher et al. 2002). BCS followed by radiotherapy is generally the preferred treatment option for early-stage breast cancer as BCS is associated with less morbidity and a better cosmetic outcome than mastectomy (NIH Consensus Conference 1991). Several population-based studies in the United States and Canada have actually reported poorer survival for patients who receive mastectomy compared to those who receive BCS plus radiotherapy (Agarwal et al. 2014; Fisher et al. 2015). About 63% of patients with stage I or II disease undergo breast-conserving surgery with or without adjuvant radiation therapy and 33% undergo mastectomy, according to data from the American Cancer Society, and the National Surgical Quality Improvement Program (NSQIP), Surveillance, Epidemiology, and End Results (SEER) program, and National Cancer Database (NCDB) (American Cancer Society 2019; Nelson et al. 2022).

The objective of BCS is to completely resect the tumor while maintaining the cosmetic appearance of the breast. Routine lumpectomy procedures involve excision of the primary specimen, followed by additional tissue resection (“shaves”) guided by intraoperative assessments such as palpation and specimen radiography. Histopathologic analysis of the outer margins of the excised tissues is used to assess the comprehensiveness of tumor resection, and positive margins are one of the primary prognostic factors for ipsilateral breast tumor recurrence (Park et al. 2000; Moran et al. 2014; Morrow et al. 2016). It is general practice that positive margins be addressed by additional tissue resection, because the increased risk of ipsilateral breast tumor recurrence associated with positive margins is not eliminated by radiotherapy or systemic therapy (Gennaro et al. 2001). Margin assessment by permanent section histopathology is completed days after the initial BCS, therefore resection of additional tissue requires an additional surgery. Approximately 20% to 40% of the patients who undergo BCS will require re-excision for positive margins determined by pathology or warrant subsequent mastectomy to achieve a definitive negative margin (Houssami et al. 2014). Re-excision is associated with greater morbidity, patient anxiety, poorer cosmetic outcome, delayed initiation of adjuvant therapies, and increased medical cost (Olsen et al. 2015). Therefore, improved intraoperative imaging tools for detection of positive margins are needed.

Currently, no FDA-approved intraoperative technology is available that directly examines the lumpectomy cavity for residual cancer after the main specimen is removed in BCS. Instead, perioperative techniques to infer the presence of residual tumor or identify positive margins all rely on ex vivo specimen analysis. In addition, no drugs are approved in the United States for intraoperative assessment of margins in breast cancer surgery.

Radiographic approaches create mammographic images in which contrast is based on x-ray beam attenuation through tissues. Prior to surgery, mammography can be used to guide placement of a surgical wire or other marker to localize the center of the apparent breast lesion. Intraoperatively during BCS, specimen mammography can be used to verify that the lesion appears to have been completely excised (Kaufman et al. 2007). However, these approaches are limited to findings that can be visualized on mammography, and they cannot assess margin status at the cellular level due to resolution limits.

Devices have been developed to determine if sampled tissue is malignant or benign based on differences in electromagnetic scattering, reflectance, and absorbance properties. As an example, MarginProbe is an FDA-approved device using radiofrequency spectroscopy, indicated as an adjunctive diagnostic tool for identification of cancerous tissue at the margins of the main ex vivo lumpectomy specimen following primary excision. Drawbacks of MarginProbe include relatively low sensitivity and specificity, the requirement for user-guided spot scanning (Maloney et al. 2018), and limitation to evaluation of the main lumpectomy specimen.

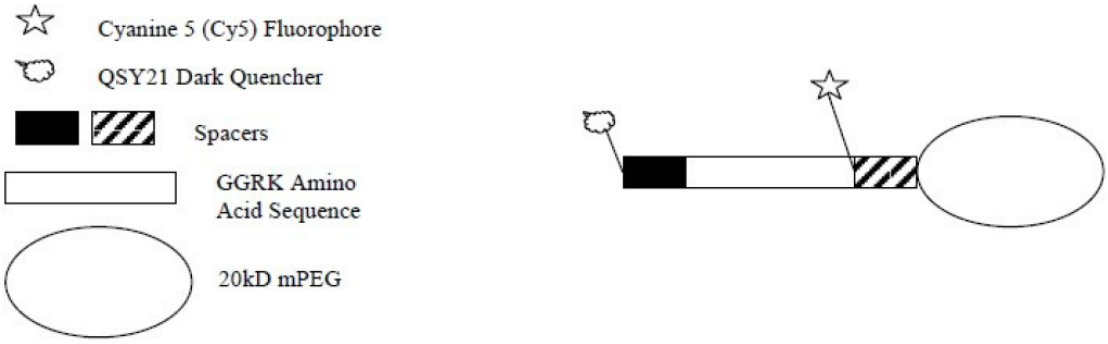
Histopathology methods for margin detection assess the microscopic cellular structure of tissue. Permanent section histopathology currently serves as the gold standard for margin assessment, however, as discussed above, it cannot be used intraoperatively. Frozen section histopathology and touch cytology can be performed rapidly enough to be incorporated into BCS workflow. Their main disadvantages beyond time needed to process and analyze the specimens, with resulting longer surgery/anesthesia time, are lower sensitivity relative to permanent section histopathology and need for additional trained personnel.

While not based on intraoperative margin assessment, the operative practice of comprehensive shaving should also be mentioned. This approach involves removing a thin rim of tissue from all available surfaces of the resection cavity after the surgeon has completed removal of the tumor per SoC. Comprehensive shaves can reduce the positive margin rate at the expense of additional removal of normal tissue.

2.2 Pertinent Drug Development and Regulatory History

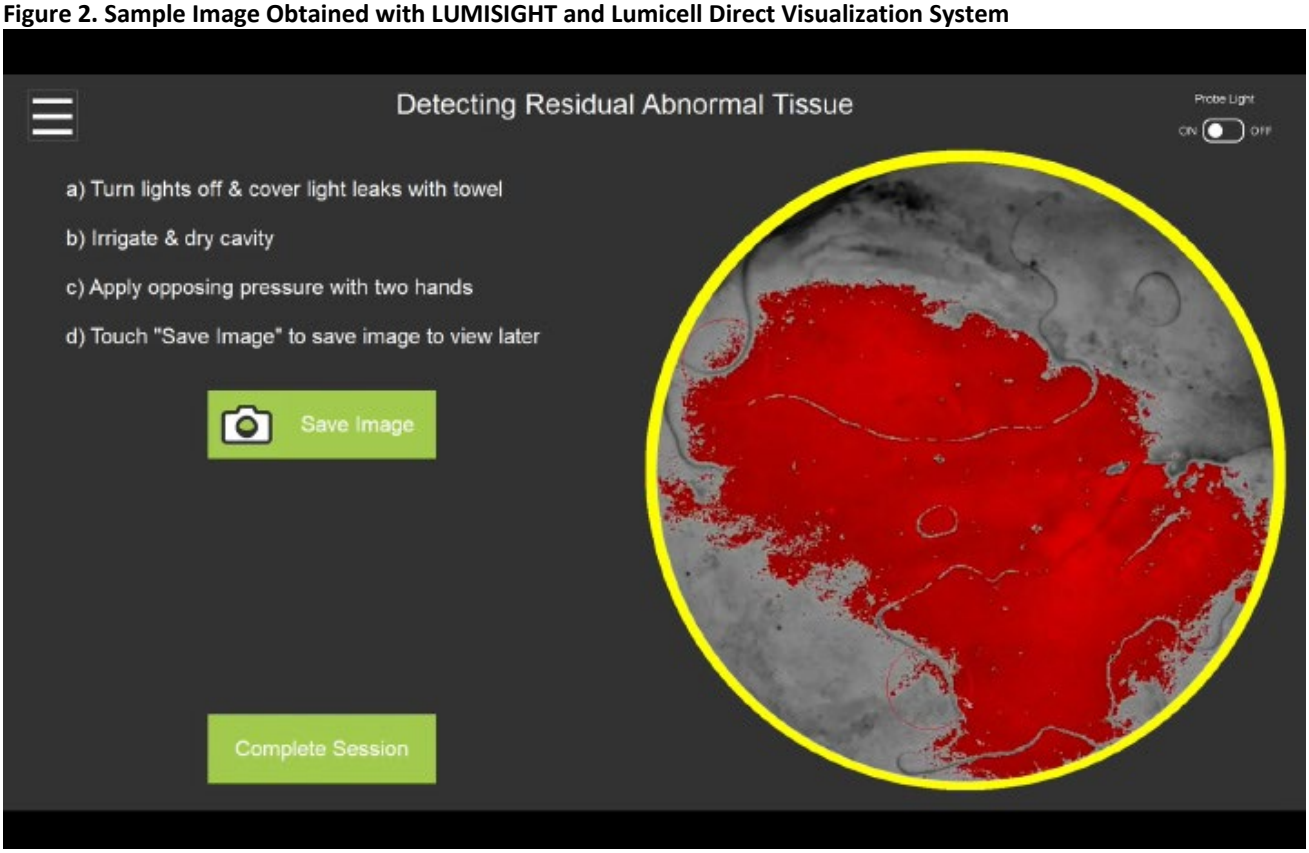
LUMISIGHT is a new molecular entity which contains a fluorophore and a quencher connected by a peptide backbone (Figure 1). LUMISIGHT is optically inactive as administered and produces a fluorescent signal after its peptide backbone is cleaved by enzymes, including cathepsins and matrix metalloproteases, which have higher activity in and around tumor and tumor-associated cells than normal cells. The fluorescence signal from cleaved pegulicianine is detected by the Lumicell DVS, which displays images and highlights suspected tissue containing cancer (Figure 2). Refer to the Appendix (6.1, 6.2) for additional background and description of the proposed work flow. The proposed indication for use 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.

Figure 1. Simplified Structural Representation of Pegulicianine



Source: Figure 1 of module 2.6.1 Pharmacology Introduction.
Abbreviations: kD, kilodaltons, mPEG, methoxypoly ethylene glycol

Figure 2. Sample Image Obtained with LUMISIGHT and Lumicell Direct Visualization System



Source: Figure 54 of Lumicell Direct Visualization System Instructions for Use.

The following is a summary of the key regulatory history of LUMISIGHT:

- September 13, 2013: The Office of Combination Products determined that LUMISIGHT and Lumicell DVS are a combination product with a device primary mode of action and designated CDRH as the lead center. After this designation, clinical development was conducted under IDE.
- March 28, 2018: Breakthrough Device designation granted for the LUM Imaging System for use in patients undergoing breast conserving surgery for breast cancer.

- October 29, 2020: Fast Track designation granted for pegulicianine for intraoperative use in patients with breast cancer to locate residual abnormal tissue during breast cancer surgery.
- The Applicant elected to submit separate marketing applications to CDER and CDRH for the drug and device components.
  - March 17, 2023: Final rolling submission to NDA 214511 for LUMISIGHT.
  - April 14, 2023: Premarket application P230014 submission for Lumicell DVS.

3 Summary of Issues for the AC

3.1 Efficacy Issues

3.1.1 Sources of Data for Efficacy

The primary evidence of effectiveness of LUMISIGHT is provided by study CL0007, a prospective, multicenter, two-arm, randomized, blinded study to evaluate efficacy of the product to identify and guide the removal of residual cancer in the lumpectomy cavity of female patients with breast cancer. Confirmatory evidence of effectiveness is provided by study CL0006, an open label, single-arm, multicenter clinical study undertaken to refine and verify the algorithm used by Lumicell DVS for detection of residual cancer tissue.

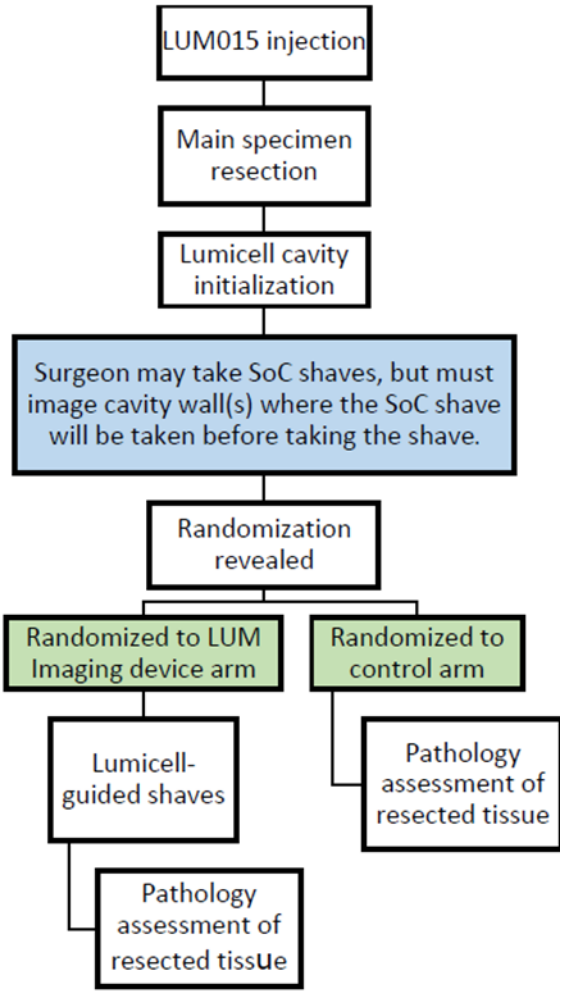
Study Protocol 0007

CL0007 enrolled adult females who had primary invasive breast cancer with or without DCIS or had DCIS only. All patients were required to be scheduled for a lumpectomy. Neoadjuvant therapy (chemotherapy, hormonal therapy, or radiotherapy) was not permitted for patients enrolled in the study. Patients scheduled for bilateral breast cancer resection, follow up surgery for positive margins from a prior lumpectomy, or a breast cancer surgery involving frozen section analysis were excluded. Patients with a history of ipsilateral reduction mammoplasty within 2 years or any history of ipsilateral breast cancer surgery, reconstruction, or implant were also excluded. Use of any dye for sentinel lymph node mapping prior to imaging with the Lumicell DVS was prohibited due to potential for interference with LUMISIGHT fluorescence detection. Patients with history of allergic reaction to PEG or any oral or IV contrast agents were also excluded.

A study design diagram is shown in Figure 3. Patients were randomized at a ratio of 10:1 between device arm and control arm. This randomization was intended to reduce the risk of surgical bias. The control arm was not planned to be large enough to support meaningful comparison of results between the study arms. All clinical staff were blinded to whether the patient was randomized to the device arm or control arm. All enrolled patients, regardless of randomization, received 1 mg/kg LUMISIGHT intravenously injected over 3 minutes, 2 to 6 hours prior to surgery. They then proceeded to their planned SoC BCS. The BCS consisted of removal of the main specimen, optionally followed by cavity shaves. SoC shaves could be selective, intended to remove specific tissues of concern to the surgeon, or comprehensive, namely applied to all orientations of the lumpectomy cavity that could be safely resected regardless of suspicion for residual malignancy. For this study, the lumpectomy cavity was divided into six orientations, anterior, posterior, medial, lateral, superior, and inferior. After removal of the main specimen and documentation of intent to remove SoC shaves, but before the surgeon took any SoC shaves, the cavity walls were imaged using the Lumicell DVS. The cancer detection algorithm of the Lumicell DVS was not active during this imaging. The resulting images were used to determine a fluorescence signal threshold that varied for each patient and would later be used by the cancer detection algorithm to mark portions of images as potentially containing cancer. Subsequently, the orientations of the cavity where SoC shaves were to be taken were imaged, again with the cancer detection algorithm turned off, and SoC shaves were performed. After the SoC BCS was completed, randomization was revealed to the study team. No additional tissue resection was performed in patients randomized to the control arm.

In patients randomized to the device arm, after completion of SoC surgery, the entire lumpectomy cavity was scanned using the Lumicell DVS, with the exception of orientations where no tissue was available to be removed. The cancer detection algorithm was on for this step, so that regions of the captured image with fluorescence signal above the threshold were highlighted on the computer monitor and displayed to the surgeon to assist in tissue resection. If the Lumicell DVS indicated an orientation was positive, the surgeon was to take a shave, termed a therapeutic shave, and repeat the imaging. Up to two therapeutic shaves could be taken from a single orientation.

Figure 3. Study Design Diagram



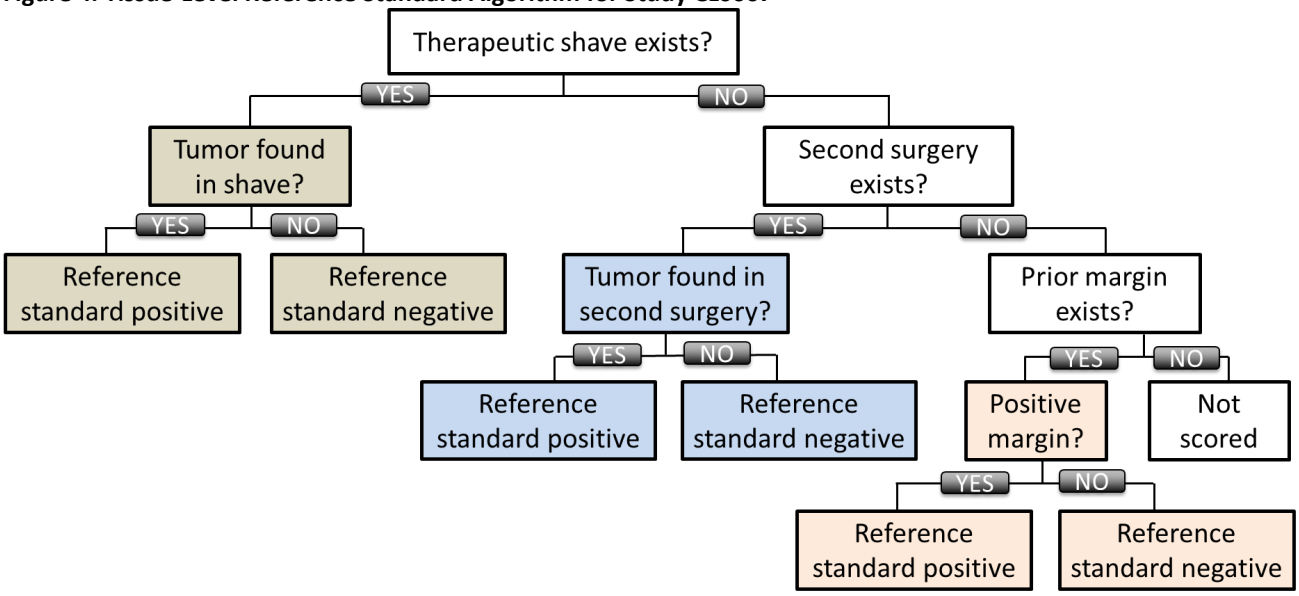
Source: CL0007 Clinical Study Report Figure 1
Abbreviations: LUM, LUMISIGHT, SoC, standard of care

After surgery was completed for patients in both the device arm and the control arm, all resected specimens were sent to the pathology laboratory at each study site for margin assessment per SoC. Pathologists were blinded to whether the shave examined was a SoC shave or a therapeutic shave.

After BCS, patients were evaluated until the investigator determined that no additional surgery was required. If follow up surgery was performed, the nature of the surgery and results of local histopathology assessments were collected, including orientation-level margin status as available.

To evaluate tissue-level sensitivity and specificity, a histopathology-based reference standard approach was developed by the Applicant and utilized in the study as presented in Figure 4. The standard was hierarchical, relying first on histopathology of therapeutic shaves if available, followed by histopathology from second surgery, followed by margin status (which was determined from histopathology of SoC shaves and lumpectomy specimens). In cases where more than one image was needed to evaluate a single orientation, if all images were negative, then the LUMISIGHT result for the entire orientation was considered negative. If one or more of the images were positive, then the entire orientation was considered LUMISIGHT positive. When multiple shaves were needed to address a single image (as distinguished from sequential shaves with imaging performed between them), if no reference standard was positive in any of the shaves, then the overall reference standard was negative. If any of the shaves were reference standard positive, then the combination of the shaves was considered reference standard positive.

Figure 4. Tissue-Level Reference Standard Algorithm for Study CL0007



Source: FDA clinical reviewer

For all resected specimens, including lump, SoC shaves, and therapeutic shaves, the Applicant employed Society of Surgical Oncology definitions (Moran et al. 2014; Morrow et al. 2016) for positive margins, such that invasive cancer with or without associated DCIS was considered to have a positive margin if cancer cells were present on an inked surface, while pure DCIS was positive if DCIS was found within 2 mm of an inked surface.

Patient-reported outcome data were collected pre-surgery and approximately 2 weeks, 3 months, and 6 months after BCS. This collection was an optional component of the study. The "Satisfaction with Breasts" survey from the Breast Conserving Therapy Scale of the BREAST-Q version 2.0 Breast Conserving Therapy Module was used.

Study Endpoints

The Applicant defined three co-primary endpoints for CL0007:

- Patient-level removal of residual cancer, defined as the fraction of patients who had cancer found in at least one therapeutic shave among all patients
- Tissue-level sensitivity (Figure 5)
- Tissue-level specificity (Figure 5)

Figure 5. Formulas for Tissue-Level Sensitivity and Specificity

		Reference Standard	
		Positive	**Negative**
LUMISIGHT imaging result	Positive	A	C
	Negative	B	D

$$Sensitivity = \frac{A}{A+B} \qquad Specificity = \frac{C}{C+D}$$

Source: FDA clinical reviewer

For the tissue-level endpoints, each of the 6 orientations of the lumpectomy cavity for each patient could contribute 0 to 3 observations. If there was no tissue that could be removed from the orientation, the orientation was not imaged and was not included in these endpoints. If there was sufficient tissue to allow a therapeutic shave (regardless of whether a therapeutic shave was taken), the number of observations included in the tissue-level endpoints for the orientation was generally equal to the number of therapeutic shaves +1.

The study protocol defined multiple secondary and exploratory endpoints. The secondary and exploratory endpoints considered most applicable to this document included:

- Conversion rate, defined as the proportion of patients with pathology-positive margins after SoC BCS for whom therapeutic shaves resulted in pathology negative margins among patients with positive margins after SoC BCS or among all patients.
- Patient-level sensitivity and specificity
- Volume of tissue removed by therapeutic shaves
- Contribution of therapeutic shave volume to total tissue removed
- Patient satisfaction survey results

The patient-level sensitivity and specificity endpoints were analyzed using two different methods for assigning the patient-level status from the tissue-level data. Each method selected the patient-level status as the first status on a priority list that matched at least one tissue-level status. The two lists were true positive (TP), false negative (FN), false positive (FP), true negative (TN) and FN, TP, FP, TN.

Statistical Analysis Plan

The primary efficacy analysis was conducted in the mITT population, defined as all patients who received LUMISIGHT except those who were not imaged with the Lumicell DVS.

The success thresholds for the co-primary endpoints were defined as 3% for patient-level removal of residual cancer, 40% for tissue-level sensitivity, and 60% for tissue-level specificity. The threshold for patient-level removal of residual cancer was selected based on estimates of local recurrence before and

after adjuvant radiation, assuming that most local recurrences are a consequence of unresected cancer during the initial surgery. The tissue-level sensitivity threshold was based on the sensitivity of histopathology margin assessment observed in a phase 2 study. The tissue-level specificity goal was set based on estimated LUMISIGHT performance and consideration of the fraction of resected tissue due to LUMISIGHT-directed shaves.

Patient-level removal of residual cancer was compared to the success threshold using the lower bound of the 95% two-sided exact confidence interval. Tissue-level sensitivity and specificity were compared using the lower bounds of two-sided 95% confidence intervals derived from generalized estimating equations to account for within-patient orientation correlations. For study success, all three co-primary endpoints were to exceed their prespecified success thresholds.

Study Protocol CL0006

CL0006 enrolled adult females who had primary invasive breast cancer with or without DCIS or had DCIS only. The study had enrollment criteria very similar to those of CL0007.

All enrolled patients received an intravenous injection of 1 mg/kg LUMISIGHT 2 to 6 hours prior to surgery and proceeded to their planned SoC BCS. The surgeon removed the main specimen with grossly negative margins according to his or her institution's SoC practice. The surgeon could remove additional tissue based on intraoperative examination of the main specimen by methods including, but not limited to, palpation, radiographic imaging, or visual examination. Some surgeons used comprehensive or selective shaves as part of their SoC procedure.

After SoC BCS, the surgeon imaged the tumor bed in order to establish a normal tissue baseline for the Lumicell DVS thresholding algorithm. With the thresholding algorithm applied, the surgeon scanned the tumor bed and removed therapeutic shaves based on the results of the Lumicell DVS. Unlike CL0007, there was no control arm, and all patients had LUMISIGHT-directed surgery. No more than two therapeutic shaves were allowed for each orientation.

All the resected tissues were to be handled and processed for margin assessment following the institution's practices for BCS. The hierarchical approach to determine the reference standard on a per image level was the same approach used in CL0007. The rules for handling multiple images for one shave and multiple shaves for one image were also the same as those in CL0007.

No hypothesis testing was specified in the study protocol. Post hoc analyses of efficacy endpoints similar to those of study CL0007 were performed.

In addition, the Applicant conducted an interim analysis to refine the Lumicell DVS tumor detection algorithm. The updated algorithm was then incorporated into the study and additional patients were enrolled. The interim analysis was performed on 83 patients. An additional 44 patients were imaged using the original algorithm, and the final 103 patients were imaged using the updated algorithm. The updated algorithm was used for CL0007 and is proposed for use in the to be marketed product.

3.1.2 Efficacy Summaries

3.1.2.1 Study CL0007

Patient Disposition

A total of 490 patients gave informed consent. Among them, 406 patients received LUMISIGHT and were included in the safety population. Fourteen patients were withdrawn from the study after injection of LUMISIGHT but before randomization. Among these, seven patients withdrew due to adverse events (AEs), two due to device issues, one because the surgical incision was too small for the device, three because of blue dye injection prior to imaging, and one patient had a prior ipsilateral procedure. A total of 392 patients were randomized to either the device arm (n=357) or the control arm (n=35).

Table of Demographic Characteristics

Patient demographics are presented in Table 1. Overall, demographic characteristics of the enrolled patients were generally representative of the population of newly diagnosed patients with breast cancer in the US. The median age at breast cancer diagnosis in the Surveillance Epidemiology and End Results data is 63 years (Howlader et al. 2021), similar to the median age of patients in this study. Fewer Black or African American patients were present than expected based on 2022 Census data (US Census Bureau 2022).

Table 1. Table of Demographics

Demographic	Safety Analysis Population (n=406)	Modified Intent-to-Treat Population (n=357)	Control Population (n=35)
Age, years			
Mean (SD)	62.3 (9.7)	62.4 (9.6)	61.6 (9.9)
Median (range)	64 (36-83)	64 (36-83)	62 (37-82)
<65 (n, %)	211 (52)	184 (52)	19 (54)
≥65 (n, %)	195 (48)	173 (48)	16 (46)
≥75 (n, %)	35 (9)	30 (8)	2 (6)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	0	1 (3)
Asian	22 (5)	22 (6)	1 (3)
Black or African American	26 (6)	22 (6)	4 (11)
Native Hawaiian or Pacific Islander	1 (<1)	1 (<1)	0
White	337 (83)	297 (83)	27 (77)
Other	4 (1)	4 (1)	0
Unknown or not reported	15 (4)	12 (3)	2 (6)
Ethnicity, n (%)			
Hispanic or Latino	12 (3)	11 (3)	1 (3)
Non-Hispanic or Latino	383 (94)	336 (94)	34 (97)
Unknown or not reported	11 (3)	10 (3)	0
BMI, kg/m^2			
Mean (SD)	29.9 (6.6)	29.8 (6.7)	31.0 (5.9)
Median (range)	29.4 (16.8-67.4)	29.4 (16.8-67.4)	30.8 (20.0-42.5)

Source: Adapted from Table 16 of CL0007 Clinical Study Report and FDA clinical reviewer
Abbreviation: BMI, body mass index

Other Baseline Characteristics

As shown in Table 2, the most common tumor histology was invasive ductal carcinoma (IDC), found in approximately 70% of patients. This is comparable to the estimated United States IDC proportion of approximately 80% of patients with newly diagnosed breast cancer (American Cancer Society 2019). Lymph node status was not assessed preoperatively in most patients.

Table 2. Tumor Histology and Preoperative Lymph Node Status in CL0007

Characteristics	Safety Analysis Population (n=406)	Modified Intent-to-Treat Population (n=357)	Control Population (n=35)
Tumor histology (biopsy and/or main lumpectomy specimen)			
DCIS Only	78 (19%)	70 (20%)	6 (17%)
IDC ± DCIS	284 (70%)	249 (70%)	25 (72%)
ILC ± DCIS	41 (10%)	35 (10%)	4 (11%)
IDC + ILC	3 (<1%)	3 (<1%)	0
Preoperative lymph node status			
Lymph node (+)	10 (2%)	9 (3%)	1 (3%)
Lymph node (-)	60 (15%)	51 (14%)	7 (20%)
No lymph node biopsy	336 (83%)	297 (83%)	27 (77%)

Source: Adapted from Table 18 of CL0007 Clinical Study Report
Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma

Table 3 shows receptor status of the enrolled patient population. Around 3% of patients in the mITT population had tumors that were triple negative, defined as estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2) non-overexpressed. This is lower than reported in a study of 61309 patients diagnosed between 1999 and 2004 (Parise et al. 2009) where 13% of patients had triple negative breast cancer. Another study reported that among patients with known estrogen receptor, progesterone receptor, and HER2 status, 12% were found to be triple negative (Howlader et al. 2014). The lower incidence of triple negative status in CL0007 was likely related to its aggressive nature, resulting in more advanced disease at presentation that was less often amenable to BCS without preoperative systemic therapy.

Table 3. Tumor Receptor Status in CL0007

Characteristic	Safety Analysis Population (N=406)	Modified Intent-to-Treat Population (N=357)	Control Population (N=35)
Receptor status			
ER (+)	378 (93%)	335 (94%)	30 (86%)
PR (+)	311 (77%)	272 (76%)	28 (80%)
HER2 (+)	23 (6%)	20 (6%)	3 (9%)
Triple negative			
Yes	15 (4%)	11 (3%)	3 (9%)

Source: Adapted from Table 18 of CL0007 Clinical Study Report
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor

Most patients in the mITT population were postmenopausal (84%, 299/357), had no palpable mass (76%, 272/357), and at mammography had scattered areas of fibroglandular density (55%, 196/357) or heterogeneously dense breast tissue (39%, 140/357). The median tumor size was 1.5 cm in the mITT

population and the preoperative tumor stage was Tis in 13%, T1 in 46%, T2 in 7%, and unknown or other in 34% of mITT patients.

Efficacy Results – Co-primary Endpoints

The co-primary efficacy endpoints were patient-level removal of residual cancer and tissue-level sensitivity and specificity. Removal of residual cancer was defined as the proportion of patients who had cancer in at least one therapeutic shave among all patients in the mITT population and was reported as 27 of 357 patients (7.6%; 95% CI: 5.0%, 10.8%). The lower bound of the 95% CI exceeded the performance goal of 3%.

Because any additional tissue resection beyond SoC may result in removal of additional cancer, it is necessary to evaluate drug imaging performance to determine whether it is reasonable to ascribe the effects on cancer removal to the product. In CL0007, tissue-level sensitivity and specificity were used to assess diagnostic performance of LUMISIGHT. As shown in Table 4, the tissue-level sensitivity was 49.1% (34/69; 95% CI: 36.4%, 61.9%) and tissue-level specificity was 86.5% (1940/2277; 95% CI: 84.5%, 88.3%). Sensitivity did not meet its performance goal of 40%, while specificity exceeded its performance goal of 60%.

Table 4. Tissue-Level Performance of LUMISIGHT for Detection of Residual Breast Cancer in the Lumpectomy Cavity

		Reference Standard		
		Positive	**Negative**	**Total**
LUMISIGHT imaging result[a]	Positive	34	337	371
	Negative	35	1940	1975
	Total	69	2277	2346
Diagnostic performance[b] (95% CI)		Sensitivity 49.1% (36.4%, 61.9%)	Specificity 86.5% (84.5%, 88.3%)	

Source: Adapted from Table 25 of CL0007 Clinical Study Report.
[a] Regions of the lumpectomy cavity from which LUMISIGHT-directed shaves were taken contributed more than one image.
[b] Sensitivity and specificity were calculated using a generalized estimating equation method to account for within-patient correlations.
Abbreviation: CI, confidence interval

A total of 2346 tissues were evaluated among the patients in the mITT population. The distribution for each component of the composite reference standard is shown in Table 5. Overall, 81% (1913/2346) of tissues used the prior margin as the reference because there were no associated therapeutic shaves or second surgeries. LUMISIGHT positive tissues generally had direct histopathologic reference data, while LUMISIGHT negative tissues usually relied on the prior margin. Thus, there is potential for bias related to the reference standard. The Applicant indicated that the prior margin component of the reference standard in particular had significant limitations that could lead to both false positive and false negative results relative to direct tissue sampling of the lumpectomy cavity. Because it was mainly used for LUMISIGHT negative tissues, these limitations in the prior margin component of the reference standard would be expected to predominantly affect the relative numbers of false negative and true negative tissues. As the observed overall rate of reference standard positivity was relatively low, this would likely have greater impact on sensitivity than specificity.

Table 5. Use of the Components of the Reference Standard

Hierarchical Assessment	Total	Therapeutic Shaves n (%)	Second Surgeries n (%)	Prior Margins n (%)
All tissues	2346	365 (16%)	68 (3%)	1913 (81%)
Reference standard positives	69	34 (49%)	24 (35%)	11 (16%)
Reference standard negatives	2277	331 (15%)	44 (2%)	1902 (83%)

Source: Adapted from Table 24 of CL0007 Clinical Study Report

Among 371 LUMISIGHT positive tissues, 337 were FP, with a proportion of LUMISIGHT true positive test results of 9.2% (95% CI: 6.4%, 12.6%). The relatively large number of FP results was not associated with a unique histopathologic change. The pathologic findings observed in at least 10% of therapeutic shaves without cancer consisted of fibrocystic change (44%), unknown (24%), usual ductal hyperplasia (17%), fibroadipose only (12%), and apocrine metaplasia (11%). Note that a single shave could have more than one pathologic finding, and the percentages are not expected to add to 100%.

Subgroup analyses of the co-primary endpoints based on age and on race are presented in Table 6. The usefulness of analysis by race was limited due to the relatively small number of non-White patients in the study. Because of the limited number of Hispanic or Latino patients enrolled, analyses based on ethnicity were not performed. Because enrollment was restricted to females, analyses based on sex were not performed. No obvious clinically important differences in effectiveness related to age or race was observed. The data suggest that the lower bound of the 95% CI for each subgroup defined by age or by race exceeded the performance goal of 3%.

Table 6. Primary Endpoint Results by Age and by Race

Parameter	Patient-Level Removal of Residual Cancer	Tissue-Level Sensitivity	Tissue-Level Specificity
Age			
<65 years	8.7% (5.1%, 13.7%)	52.4% (36.4%, 68%)	83% (80.7%, 85.1%)
≥65 years	6.4% (3.2%, 11.1%)	44.4% (25.5%, 64.7%)	87.6% (85.5%, 89.5%)
Race			
White	7.1% (4.4%, 10.6%)	49.1% (35.1%, 63.2%)	86.4% (84.8%, 87.9%)
Non-white	10% (3.8%, 20.5%)	50% (24.7%, 75.3%)	79.6% (75.3%, 83.4%)

Source: FDA clinical reviewer
Note: Tissue-level sensitivity and specificity were derived using exact confidence interval estimates. Parenthetical values are 95% confidence interval estimates.

Subset analysis of the primary endpoints by type of SoC shave (Table 7) showed a trend towards higher tissue-level specificity in patients who did not receive a selective shave. The clinical significance of this observation is doubtful. Similar analyses of the other primary endpoints are limited by small size of the subgroups, but no clear difference was identified. Of note, the patient-level removal of residual cancer endpoint point estimate was not decreased in the patients who received comprehensive shaves.

Table 7. Primary Endpoint Results by Type of Standard of Care Procedure

Patients	All	Comprehensive	Selective Having SoC Shave	Selective With No SoC Shave
	357	71	165	121
Patient-level removal of residual cancer	7.6% (5%, 10.8%)	9.9% (4.1%, 19.3)	7.3% (3.8%, 12.4%)	6.6% (2.9%, 12.6%)
Tissue-level sensitivity	49% (36%, 62%)	58% (31%, 82%)	42% (26%, 60%)	54% (30%, 76%)
Tissue-level specificity	86% (85%, 88%)	83% (78%, 87%)	83% (80%, 86%)	93% (90%, 95%)

Source: Adapted from Tables 23 and 27 of CL0007 Clinical Study Report
Note: Tissue-level sensitivity and specificity were derived using GEE estimator. Parenthetical values are 95% confidence interval estimates.
Abbreviations: GEE, generalized estimating equation; SoC, standard of care

Tissue-level sensitivity and specificity by tumor histology are presented in Table 8. The number of reference standard positive tissues was too small for robust comparison of sensitivity between tumor types, though there may be a trend towards slightly lower sensitivity in patients with DCIS only. Specificity trended lower for DCIS only or IDC+DCIS than IDC alone. The clinical importance of this observation is unclear.

Table 8. Tissue-Level Performance by Tumor Histology

	All	DCIS	IDC	IDC+DCIS	IDC+ILC+ DCIS	ILC+DCIS
n Patients	356	70	164	84	3	35
Tissue-level sensitivity	49.3% (37%, 61.6%)	41.4% (23.5%, 61.1%)	47.1% (23%, 72.2%)	50% (26%, 74%)	N/A	100% (47.8%, 100%)
Tissue-level specificity	85.2% (83.7%, 86.6%)	81.2% (77.2%, 84.8%)	87.1% (84.9%, 89.1%)	83.1% (79.7%, 86.1%)	89.5% (66.9%, 98.7%)	88.8% (83.9%, 92.6%)

Source: Adapted from Table 64 of CL0007 Clinical Study Report

Note: Tissue-level sensitivity and specificity were derived using exact confidence interval estimates. Parenthetical values are 95% confidence interval estimates.

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; N/A, not applicable

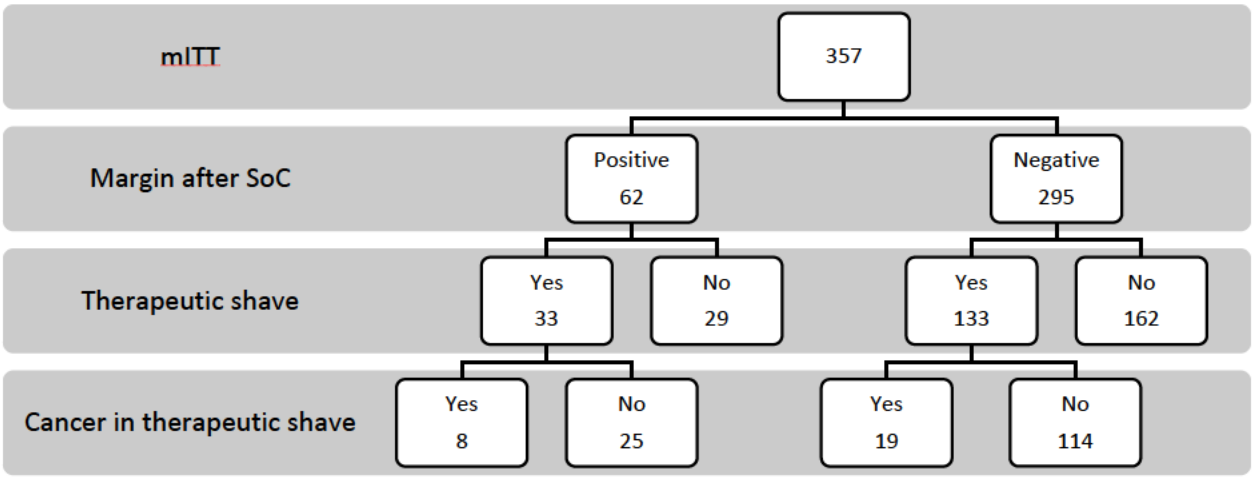
Subgroup analyses of the co-primary endpoints by mammographic breast density and receptor status were performed by the clinical team. In many cases, the resulting subgroups were too small for meaningful interpretation. Where interpretable, the analyses did not show trends that were expected to affect use of the product.

Efficacy Results – Secondary and Other Endpoints

Among the 357 patients in the mITT Population, 62 (17.4%) had positive margins after the SoC surgery, i.e., before LUMISIGHT-guided intervention. In 10 of these 62 patients (16.1%; 95% CI: 7%, 25.3%), LUMISIGHT fluorescence was found in the cavity matching all orientations with positive margins. Nine of these patients (14.5% of patients with positive margins after SoC surgery [95% CI: 5.8%, 23.3%], 2.5% of the mITT population [95% CI: 0.9%, 4.1%]) converted to negative margins after image-guided resections. A second surgery was avoided for eight of these patients due to LUMISIGHT-guided therapeutic shaves, an important outcome of the use of the product. However, eight of the nine patients who converted from positive margins after SoC surgery to negative margins after LUMISIGHT-guided shaves did not have cancer in the LUMISIGHT-guided shaves. This observation and the previously discussed relatively large number of FP therapeutic shaves raise uncertainty regarding the relative contributions of LUMISIGHT versus the overall increased number of shaves.

As shown in Figure 6, 166 (46%) of patients in the mITT population received at least one LUMISIGHT-guided shave after completion of SoC surgery. The rate of cancer being present in a therapeutic shave trended higher in patients who had positive margins after SoC surgery (8/33, 24%) than those with negative margins (19/133, 14%). It is notable that 19 of the 27 patients who had cancer in at least one therapeutic shave had negative margins after SoC surgery. Such cancer would most likely not be addressed by follow-up surgery, since without LUMISIGHT it would remain undetected. However, the clinical significance of this finding is unclear. In patients with invasive breast cancer, the frequency of radiographically occult satellite tumor foci or multifocal disease can be high, with one study based on pathologic analyses of mastectomy specimens finding that 20% of patients with invasive breast cancer ≤5 cm in diameter had another tumor focus within 2 cm of the reference tumor and 43% had another tumor focus >2 cm from the reference tumor (Holland et al. 1985). These data were considered during development of current margin recommendations (Moran et al. 2014) where evidence of decrease in ipsilateral breast tumor recurrence for margins wider than tumor on ink, which would be expected to remove some nearby disease foci, was not found for invasive breast cancer. One possible explanation for this observation is that breast radiotherapy is generally performed after BCS, often with adjuvant systemic therapies. A negative margin does not guarantee that a patient will not experience tumor recurrence, and it is possible that the removal of additional tumor from patients with negative margins by LUMISIGHT could reduce recurrence risk, but data to this effect are not presented by the Applicant.

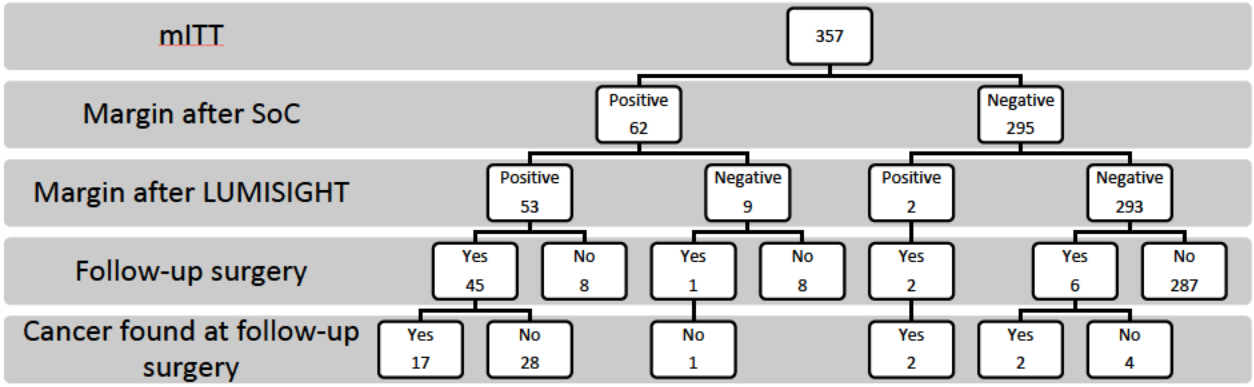
Figure 6. Distribution of Patients with Cancer in at Least One Therapeutic Shave by Standard of Care Margin Status



Source: FDA clinical reviewer
Abbreviations: mITT, modified intent-to-treat, SoC, standard of care

A total of 47 patients (13%) in the mITT population were recommended for and underwent follow-up surgeries due to final positive margins after completion of BCS, including LUMISIGHT-guided therapeutic shaves, and an additional 7 patients had follow-up surgeries for reasons other than final positive margins. The rate of cancer found in follow-up surgeries was 39% (21 out of 54). One patient who converted from a positive margin after SoC surgery to negative margin after therapeutic shaves did proceed to follow-up surgery, where no additional cancer was found (Figure 7). Two patients who converted from negative margins after SoC BCS to positive margins following removal of cancer in therapeutic shaves had a follow-up surgery, and cancer was found in both cases. Although the clinical significance of removing cancer in patients with SoC negative margins is unclear, it is reassuring that additional cancer was found at follow up surgery in both of these patients.

Figure 7. Distribution of Patients with Follow-up Surgery by Standard of Care Margin Status and by Post-LUMISIGHT Margin Status



Source: FDA clinical reviewer
Abbreviations: mITT, modified intent-to-treat, SoC, standard of care

Before removing SoC shaves, the corresponding cavity orientations were imaged with the Lumicell DVS while the tumor detection algorithm was turned off. These images were later processed with the tumor

detection algorithm and compared to the composite reference standard to obtain additional information regarding diagnostic performance. These data were collected for all patients having SoC shaves, regardless of randomization to the device or control arm. The results show a lower specificity for imaging prior to SoC shaves versus imaging after SoC shaves are obtained, 86.5% versus 66.4% (Table 9). The Applicant hypothesized that use of the Lumicell DVS with the tumor detection algorithm disabled led to removal of SoC shaves from areas other than the imaged region. It is not clear why disabling the tumor detection algorithm would alter alignment of imaging and shave, but we note that the proposed use of the product is after SoC shaves are obtained, therefore the specificity prior to SoC shaves is not directly relevant. Further, the consequence of lower specificity should the product be used off label in this manner is the removal of a relatively small amount of non-cancerous tissue.

Table 9. Tissue-Level Sensitivity and Specificity of Imaging Obtained Prior to Standard of Care Shaves

Parameter	Prior to SoC Shaves (693 Images From 391 patients)	After SoC Shaves (2346 Images From 356 Patients)	All Images Combined (3039 Images From 391 Patients)
True positive	44	34	78
False positive	195	337	532
False negative	54	35	89
True negative	400	1940	2340
Sensitivity	44.9% (35.3%, 54.9%)	49.1% (36.4%, 61.9%)	46.3% (38%, 54.8%)
Specificity	66.4% (61.8%, 70.7%)	86.5% (84.5%, 88.3%)	83.1% (81.1%, 84.9%)

Source: Adapted from Tables 26 and 47 of CL0007 Clinical Study Report
Notes: Patients in both the device arm and control arm are included in this table. Sensitivity and specificity were derived using generalized estimating equations estimation. Parenthetical values are 95% confidence interval estimates.
Abbreviation: SoC, standard of care

Patient-level sensitivity and specificity analyses were performed based on the tissue-level results (Table 10). This requires a method for assigning a patient-level result when tissue-level results are discordant. Two hierarchical methods were used, one where FN results were prioritized over TP results, emphasizing complete identification of tumor in the cavity, and one where TP results were prioritized over FN, emphasizing the identification of any cancer. In both methods, FP was prioritized over TN. Patient-level specificity is equivalent for both methods at 58% (95% CI: 52%, 63%), and as expected it is lower than tissue-level specificity because a patient was required to have only TN tissue-level results to be assigned TN status. Patient level sensitivity is 44% (95% CI: 30%, 59%) when FN results are prioritized and 54% (95% CI: 39%, 68%) when TP results are prioritized. The difference in these values indicates that when a patient has more than one tissue containing tumor, the product may not identify all positive tissues. This is in keeping with the observed tissue-level sensitivity. The fraction of patients who had at least one FN tissue was 7.8% (95% CI: 5.1%, 10.6%) and the fraction of patients who had at least one FP tissue was 43.4% (95% CI: 38.3%, 48.6%). Among the 27 patients who had cancer found in at least one LUMISIGHT-directed shave, the fraction of patients who had at least one FN tissue was 18.5% (95% CI: 3.9%, 33.2%) and the fraction of patients who had at least one FP tissue was 59.3% (95% CI: 40.7%, 77.8%). In the mITT population, 38.9% (95% CI: 33.9%, 44%) of patients had no TP tissue and at least one FP tissue. A total of six patients had at least one TP tissue with no FP or FN tissues.

Table 10. Patient-Level Sensitivity and Specificity in the mITT Population Estimated Based on Tissue-Level Data

Parameter	False Negative > True Positive	True Positive > False Negative
True positive	22	27
False positive	130	130
False negative	28	23
True negative	176	176
Patient-level sensitivity	44% (30%, 59%)	54% (39%, 68%)
Patient-level specificity	58% (52%, 63%)	58% (52%, 63%)

Source: Adapted from Tables 52 and 54 of CL0007 Clinical Study Report and Table 17 of the Sponsor Briefing Document
Note: Parenthetical values are 95% exact binomial confidence interval estimates.
Abbreviation: mITT, modified intent-to-treat

LUMISIGHT use is expected to increase the volume of resected tissue compared to SoC BCS, which has the potential to negatively impact cosmesis. This is particularly concerning due to the substantial number of FP therapeutic shaves observed in CL0007. The Applicant performed several secondary analyses to examine the effect of LUMISIGHT on resection volume and cosmesis. As shown in Table 11, the mean total resection volume for SoC BCS in the mITT Population was 89 mL, and the SoC resection volume was similar between patients with and without therapeutic shaves. Among the 166 patients who had at least one therapeutic shave, the mean volume of therapeutic shaves was 21.8 mL, representing 25% of the SoC resection volume and 20% of the total volume for the combined resection. For comparison, the median additional resected volume in a multicenter, randomized trial of comprehensive shaves was 36.1 mL and the SoC resection volume was 61.6 mL, with no increase in immediate surgical complications such as seroma (Dupont et al. 2021).

Table 11. Resected Tissue Volumes in CL0007

Variable	All Patients (N=357)	Therapeutic Shave (N=166)	No Therapeutic Shave (n=191)
SoC BCS volume (mL)			
Mean (SD)	89 (93.7)	86.8 (70)	90.9 (110.4)
Median (min-max)	66.4 (5.5-963)	70.6 (6-601.4)	63 (5.5-963)
Therapeutic shave volume (mL)			
Mean (SD)	10.1 (17.5)	21.8 (20.1)	-
Median (min-max)	0 (0-126.7)	15.6 (0.7-126.7)	-
Total volume (mL)			
Mean (SD)	99.1 (97.3)	108.6 (79)	90.9 (110.4)
Median (min-max)	77.5 (5.5-963)	90 (13.7-625.8)	63 (5.5-963)
Ratio of therapeutic shave contribution (%)			
Mean (SD)	9.4 (14.1)	20.3 (14.5)	0
Median (min-max)	0 (0-81.3)	16.7 (1.7-81.3)	0

Source: Tables 33 and 34 of CL0007 Clinical Study Report and FDA clinical reviewer
Abbreviations: BCS, breast-conserving surgery; max, maximum; min, minimum; SoC, standard of care; SD, standard deviation

Among the 357 patients in the mITT population, 255 (71%) consented to participate in the patient reported outcome portion of the study. Survey responses after surgery deviated from the intended

collection timepoints, and the timeframes were reclassified according to the number of days after the surgery in which the survey was completed.

1. Presurgery: Survey completed any time before the surgery
2. Initial postsurgical follow-up: Survey completed within 45 days after the surgery
3. Three months: Survey completed between 45 and 135 days after the surgery
4. Six months: Survey completed more than 135 days after the surgery

Table 12 shows the completion rate for the survey among the mITT population. As expected, particularly given the optional nature of the survey and the late addition of the 6-month time frame to the protocol, relatively few patients responded by 6 months. However, the responders were roughly evenly divided between patients who had and did not have a therapeutic shave at all time points. Patients who did not have a therapeutic shave can serve as a surrogate for expected survey results in patients who have SoC surgery, at least for questions related to additional tissue resection.

Table 12. Survey Completion by Time for the Modified Intent-to-Treat Population

Time Frame	Number of Patients Completing Survey (% of mITT)	Number of Patients Completing Survey Who Had No Therapeutic Shave	Number of Patients Completing Survey That Had at Least One Therapeutic Shave
Presurgery	161 (45%)	84	77
Follow-up	154 (43%)	77	77
3 months	126 (35%)	58	68
6 months	50 (14%)	23	27

Source: Table 4-2 of Addendum to CL0007 Clinical Study Report
Abbreviation: mITT, modified intent-to-treat

The majority of the patients responded 'Very Satisfied' (score 3) or 'Somewhat Satisfied' (score 4) for all questions and timeframes. This is reflected in the generally high combined scaled scores (range 0 to 100) shown in Table 13. There is a trend to slightly lower scaled scores in the patients who had therapeutic shaves than those without therapeutic shaves for all time periods, including the pre-surgical baseline. Examination of the individual item responses did not reveal clear differences between patients who did and did not have therapeutic shaves. Weakness of these data include the small number of respondents and the self-selection for participation in this portion of the study. However, the available results do not suggest that additional tissue resection driven by LUMISIGHT worsened cosmetic outcome.

Table 13. Scaled Patient Satisfaction Score by Therapeutic Shave Status

Time Frame	No Therapeutic Shave		At Least One Therapeutic Shave	
	N	Mean (95% CI)	N	Mean (95% CI)
Presurgery	84	64.1 [58.7, 69.5]	77	61.3 [56.5, 66.2]
Follow-up	77	76.4 [71.4, 81.5]	77	73.9 [69.4, 78.3]
3 Months	58	73 [66.6, 79.4]	68	69.4 [64.1, 74.7]
6 Months	23	75.4 [63.5, 87.4]	27	71 [62.7, 79.4]

Source: Table 5-2 of Addendum to CL0007 Clinical Study Report
Abbreviations: CI, confidence interval

3.1.2.2 Study CL0006

The co-primary efficacy endpoints of CL0007 were applied to CL0006 retrospectively. As noted in Section 3.1.1, the Lumicell DVS tumor detection algorithm was modified based on results of an interim analysis

of CL0006. The patients from the mITT population who were imaged prospectively with the updated algorithm, which was also employed in CL0007, were termed the validation set (n=103). Because reference standard data collection was influenced by whether a therapeutic shave was positive or negative, and thus the algorithm used, we focus on the validation set here. However, the Applicant also presented retrospective analyses using the updated algorithm for the patients imaged prior to completion of the interim analysis (extended training set, n=127).

Removal of residual cancer, defined as the proportion of patients who had cancer in at least one therapeutic shave among all patients, was 9 of 103 (8.7%; 95% CI: 4.1%, 15.9%) for the validation set. In the extended training set, 17 of 127 patients (13.4%; 95% CI: 8%, 20.6%) had removal of residual cancer. The rate in the validation set is similar to that seen in CL0007 (7.6%; 95% CI: 5%, 10.8%). The significance of the trend to a higher rate in the extended training set is unknown. As shown in Table 14, in the validation set the tissue-level sensitivity was 63.5% (95% CI: 41%, 81.4%) and specificity was 80.2% (95% CI: 75.8%, 84%). The sensitivity estimate trended higher than was observed in CL0007, but given the relatively small number of reference standard positive tissues in both studies, the significance of this trend is not clear. The specificity estimate was lower, but the difference in point estimates was not large, 6.3%, and the clinical consequence of this difference is doubtful.

Table 14. Tissue-Level Performance of LUMISIGHT for Detection of Residual Breast Cancer in the Lumpectomy Cavity in CL0006

Parameter	Validation Set–Prospective Refined Algorithm (Patients N=103)	Extended Training Set–Retrospective Refined Algorithm (Patients N=127)
True positives	16	27
False positive	149	301
False negative	9	10
True negatives	545	527
Tissue-level sensitivity (95% CI)	63.5% (41%, 81.4%)	72.9% (56%, 85%)
Tissue-level specificity (95% CI)	80.2% (75.8%, 84%)	64.6% (60.3%, 68.7%)

Source: Adapted from Table 5 of Integrated Summary of Effectiveness
Note: Sensitivity and specificity were calculated using a generalized estimating equation method to account for within-patient correlations. Parenthetical values are 95% confidence interval estimates.
Abbreviation: CI, confidence interval

3.1.3 Efficacy Considerations

CL0007 did not meet the predefined success criteria due to its failure to exceed the threshold of 40% for tissue-level sensitivity. The lower bound of the 95% confidence interval was reported as 36.4%, a 3.6% absolute difference. For several reasons, we believe that CL0007 provides evidence of effectiveness despite this limitation. The 40% threshold was selected by the Applicant based on estimated performance of margin pathology from results of earlier studies of LUMISIGHT. While the threshold was considered clinically meaningful, there was no consideration of whether a lower threshold might be justifiable. Moreover, the difference between the estimated sensitivity and the threshold was small. Finally, the intent of the tissue-level sensitivity endpoint is to assess whether LUMISIGHT can detect residual breast cancer in the lumpectomy cavity. True positive detection is expected to result in cancer excision from the orientation. Therefore, the successful patient-level endpoint of removal of residual cancer is supportive because it measures a closely related concept. While higher values would be desirable, taken together the observed sensitivity and specificity demonstrate adequate diagnostic

performance of the drug for imaging cancer in the lumpectomy cavity. This is evidenced by a tissue-level accuracy under conditions of the trial of 84.1% (95% CI: 82.6%, 85.6%), which exceeds the 50% expected from a random binary outcome test. Overall, the clinical and statistical teams find that CL0007 is an adequate and well-controlled study that demonstrates the effectiveness of LUMISIGHT for detecting cancer in the lumpectomy cavity following SoC surgery.

We do not consider CL0006 to be an adequate and well-controlled study for regulatory purposes. The study lacked prespecified effectiveness endpoints and success thresholds, as well as a control arm to minimize the potential for decreasing SoC tissue excision by surgeons. An interim analysis was performed to adjust the tumor detection algorithm of the Lumicell DVS. The patients imaged with the initial algorithm were retrospectively reanalyzed with the updated algorithm, but the results had potential for bias from prior analyses and from the use of the imaging algorithm to alter reference standard data collection. However, the results from patients imaged prospectively with the updated algorithm were obtained from a clinically relevant population and generally aligned with the results of the adequate and well-controlled study. These data are adequate to serve as confirmatory evidence of effectiveness.

It is important to consider how successful imaging of breast cancer in the lumpectomy cavity might affect surgical outcomes to determine the magnitude of clinical benefit. Patients who had positive margins at the conclusion of SoC BCS but were converted to negative margins by LUMISIGHT are expected to have substantial benefit through avoidance of a second surgery. In CL0007, 9 patients (3% of mITT population) converted to negative final margins. However, 8 of these patients did not have cancer in the LUMISIGHT-guided shaves. The Applicant hypothesizes that this phenomenon might be due to the presence of cancer-associated cells in the tissue shaves or diffusion of LUMISIGHT-cleaving enzymes or activated LUMISIGHT away from the tumor and postulates that this will contribute to the completeness of tumor resection and achievement of an adequate normal tissue margin. However, no data were presented to support this hypothesis. The uncertainty regarding how many conversions to negative margins were attributable to accurate detection of cancer by LUMISIGHT is an important issue in assessing the magnitude of LUMISIGHT benefit.

In patients who do not convert from positive to negative margins, the benefit of removing additional cancer is not straightforward to demonstrate. The prevalence of imaging-occult, multifocal or multicentric disease can be high in patients amenable to BCS (Holland et al. 1985). In this context, obtaining a wide margin around the index tumor might remove additional cancer, but data are lacking to show decreased tumor recurrence rates with wide tumor margins in patients with invasive breast cancer (Moran et al. 2014). In part these results may be related to the modern breast cancer therapy use of a multimodality approach, generally combining radiotherapy with BCS and often also including systemic chemotherapy or hormonal therapy (National Comprehensive Cancer Network Inc. 2023). It seems likely that cancer removal rate might overestimate the rate of improvement in more direct measures of patient benefit such as cancer recurrence rate and patient survival.

While tissue-level specificity substantially exceeded the predefined success threshold in CL0007, the relatively low number of lumpectomy cavity orientations identified as containing cancer meant that a large number of FP therapeutic shaves were obtained. The risk of removing this non-malignant tissue is mainly to cosmetic outcome of the procedure. The Applicant presented data showing that the volume of tissue removed in LUMISIGHT-directed shaves, averaged among patients with at least one therapeutic shave, was similar to the volume removed using comprehensive shaves. Moreover, in a subset of

patients, similar satisfaction with cosmetic outcome of the surgery was reported by patients who had therapeutic tissue shaves and those who did not. Therefore, the risk of adverse cosmetic outcome appears negligible based on these results.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

Safety data were collected from 8 completed and ongoing studies of LUMISIGHT in patients with breast cancer, soft tissue sarcoma, prostate cancer, and gastrointestinal cancers. A cardiovascular safety study enrolling healthy volunteers was also considered in the safety analysis.

In the submitted safety data, 710 patients with breast cancer, 56 patients with other cancers, and 24 healthy volunteers each received a single dose of LUMISIGHT for a total of 790 patients. LUMISIGHT doses of 0.5 mg/kg (n=32), 1 mg/kg (n=732), 1.5 mg/kg (n=14), 2 mg/kg (n=6), or 4 mg/kg (n=6) were administered by IV injection over 3 minutes.

Patients with any cancer who were intended to receive the to-be-marketed dose of 1 mg/kg compose the primary safety analysis population. This population has 726 patients, including 703 (97%) patients with breast cancer, 15 patients with gastrointestinal cancers, 5 patients with sarcoma, and 3 patients with prostate cancer. Healthy volunteers are excluded because they may have less exposure to the cleavage products of LUMISIGHT.

3.2.2 Safety Summary

The most commonly observed adverse event in the safety population, occurring in 85% of the primary safety analysis population, was chromaturia. This is ascribed to urinary excretion of the drug, which is dark blue in color.

Hypersensitivity reactions, including anaphylaxis, were the second most commonly observed AE, occurring in 4.8% (35/726; 95% CI:[1] 3.4%, 6.6%) of patients, and are discussed further in section 3.2.3. Among these, 1.4% (10/726; 95% CI: 0.7%, 2.5%) of patients had reactions assessed as related to investigational product (IP) by the study investigators. AEs adjudicated as anaphylaxis by FDA occurred in 0.6% (4/726; 95% CI: 0.2%, 1.4%) of patients.

Other AEs were each reported in less than 1% of patients and included skin discoloration after extravasation, nausea, dyspnea, pyrexia, and vomiting. AEs leading to study discontinuation occurred in 8 patients (1.1%; 95% CI: 0.5%, 2.2%), and 3 of these patients experienced serious AEs. No LUMISIGHT-related deaths have been reported.

3.2.3 Safety Considerations

Safety Review Considerations

Evaluation of hypersensitivity AEs, including anaphylaxis, and attribution of these events to LUMISIGHT are challenging due to the lack of an unexposed concurrent control group in the trials for event rate comparison. All enrolled patients were exposed to LUMISIGHT, and thus it is unknown how frequently these events would occur in patients without this exposure. In addition, patients experienced numerous confounding interventions, including presurgical fasting, presurgical procedures such as wire placement, presurgical medication administration including antibiotics, and surgery.

Compounding this analytical challenge are the typical residual uncertainties in adjudication of clinical trial data for anaphylaxis, for example, the lack of reliable biomarkers and the limited information available in the clinical case narratives. The clinical diagnosis of anaphylaxis can be challenging due to the breadth of possible clinical manifestations and complex pathogenesis.

Some of these AEs, whether those adjudicated as anaphylaxis or those less serious AEs identified by the Hypersensitivity FDA medical query (FMQ), may occur via mechanisms other than IgE or immunologic pathways, as discussed below. Additionally, the intended clinical use of this product for single administration in a medically supervised setting must be noted when considering the risk of hypersensitivity reactions, including anaphylaxis.

Safety Results

Among the 726 patients in the primary safety analysis population, 35 (5%) patients were identified by the FMQ for Hypersensitivity (Broad), as shown in Table 15. Of these patients, the majority (18/35; 51%) experienced AEs of mild severity. Various types of rashes occurred in 19/35 (54%) patients. FDA examined the subset of these events occurring on Study Day 1 (when LUMISIGHT was administered), as the timing of these events may be consistent with immediate type hypersensitivity or infusion-related reactions, which are of greatest interest. A total of 16 (2%) patients had event(s) occurring on Study Day 1. Of the events occurring on Study Day 1, the median duration was 1 day (mean 6 days).

Table 15. AEs Identified by Hypersensitivity (Broad) FMQ, Regardless of Relatedness, by AE Onset Day, in the Primary Safety Analysis Population (n=726)

FMQ or Preferred Term	Number (%)* of Patients	Number (%)* of Patients with Event(s) Occurring on Study Day 1
Hypersensitivity FMQ	35 (4.8%)	16 (2.2%)
Rash	19 (2.6%)	4 (0.6%)
Pruritus	8 (1.1%)	4 (0.6%)
Anaphylactic reaction**	4 (0.6%)	4 (0.6%)
Hypersensitivity	3 (0.4%)	3 (0.4%)
Urticaria	2 (0.3%)	1 (0.1%)
Drug hypersensitivity	1 (0.1%)	1 (0.1%)
Edema	1 (0.1%)	0
Swollen tongue	1 (0.1%)	1 (0.1%)
Wheezing	1 (0.1%)	0

Source: FDA clinical reviewer; Applicant's Information Request response received January 23, 2024
The Hypersensitivity (Broad) FMQ captures patients with events meeting the FMQ (Broad and Narrow) criteria with start dates within 7 days of each other. The list of AE preferred terms (PTs) in and algorithm for the FMQ are publicly available (https://www.regulations.gov/document/FDA-2022-N-1961-0001).
"Rash" includes PTs erythema, rash maculopapular, rash erythematous.
*Percentage of the Primary Safety Analysis Population (n=726).
**One patient with assigned PT "Hypersensitivity" is reflected here as "Anaphylactic reaction" because the event was adjudicated as anaphylaxis by the FDA reviewer.
Abbreviations: AE, adverse event; FMQ, FDA medical query, PT, preferred term.

Considering only hypersensitivity reactions deemed related to LUMISIGHT administration by the investigator, 10 patients were identified, as shown in Table 16. Attribution of these reactions as related to LUMISIGHT may be biased by the open-label nature of the drug administration, but as there is not a concurrent control group in this trial, it may be a useful component of risk evaluation in this application. In terms of investigator-assigned severity, five (50%) patients had moderate reactions (hypersensitivity

(n=2), rash maculopapular (n=2), urticaria (n=1)), four (40%) severe (anaphylaxis (n=3) and hypersensitivity n=1)), and one (10%) life-threatening (anaphylaxis).

Table 16. AEs Identified by Hypersensitivity (Broad) FMQ, Deemed Related to IP by the Study Investigator, in the Primary Safety Analysis Population (n=726)

FMQ or Preferred Term	Number (%) of Patients
Hypersensitivity*	10 (1.4%)
Anaphylactic reaction**	4 (0.6%)
Hypersensitivity	3 (0.4%)
Rash maculopapular	2 (0.3%)
Pruritus	1 (0.1%)
Urticaria	1 (0.1%)

Source: FDA clinical reviewer
*FDA's review identified 10 patients with hypersensitivity events deemed related by the investigator, while the Applicant reports 9 patients in their Advisory Committee briefing document. The Applicant does not include the PT Rash maculopapular in their analysis.
**One patient with assigned PT Hypersensitivity is reflected here as Anaphylactic reaction because the reaction was adjudicated as anaphylaxis by the FDA reviewer.
Abbreviations: FMQ, FDA medical query, PT, preferred term.

Adverse events adjudicated by FDA as anaphylaxis occurred in four patients (0.6%; 95% CI: 0.2%, 1.4%). Case narratives were provided to FDA for SAEs and AEs resulting in study discontinuation. The narratives describing possible cases of anaphylaxis were reviewed and adjudicated. When adjudicating, FDA applied the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criterion number 1 (see section 6.3) as LUMISIGHT was not a likely or known allergen for the patient. The NIAID/FAAN framework does not grade the severity of a reaction, as anaphylactic reactions are by definition systemic and unpredictable; as such, they are considered potentially life-threatening. Available narrative information for the four events adjudicated as anaphylaxis by FDA is summarized in Table 17 and provided in more detail in section 6.4.

Table 17. Summary of Reactions Adjudicated by FDA as Anaphylaxis

Patient Identifier (Age, years)	Onset	AE PT	Signs and Symptoms	Action Taken	Outcome
1 (73)	During injection	Anaphylactic reaction	Dyspnea; chest pain; flushing of face and upper body; generalized rash; apnea; cyanosis; nausea; hypotension. Tryptase, histamine, and total complement not measured.	IP administration stopped. Treatment: Bag-mask assisted ventilation. Epinephrine IV 4 doses and continuous drip; IV fluid boluses; diphenhydramine; glucocorticoid. ICU admission. Study withdrawal.	Recovery in 2 hours. Discharged home the following day.
2 (47)	During injection	Hypersensitivity	Hypotension; generalized erythema; nausea and vomiting. Tryptase and histamine elevated; total complement normal.	IP administration stopped. Treatment: IV fluids, diphenhydramine, ondansetron. Placed in reverse Trendelenburg. Study withdrawal.	Recovery in 25 minutes
3 (40)	During injection	Anaphylactic reaction	Dyspnea; lip angioedema; tingling in tongue, hands, and feet; eye redness; "black spots" in vision; nausea and vomiting. Tryptase and total complement normal; histamine elevated.	IP administration stopped. Treatment: diphenhydramine; glucocorticoid; ondansetron. Study withdrawal.	Recovery in 20 to 30 minutes; however, tingling of feet lasted 2 hours
4 (61)	Immediately after injection	Anaphylactic reaction	Hypotension; itching and numbness of hands, feet, and lips. Tryptase, histamine, and total complement normal.	Treatment: IV fluids. Placed in reverse Trendelenburg.	Recovery in 30 minutes

Source: FDA clinical reviewer
Abbreviations: AE, adverse event; ICU, intensive care unit; IP, investigational product; IV, intravenous; PT, preferred term

The four events summarized in Table 17 meet accepted criteria for anaphylaxis. After the first reported anaphylactic reaction occurred in trial CL0006 (Patient 1), the Applicant amended the clinical protocols to add blood collection for tryptase, histamine, and total complement levels in suspected cases; baseline levels were not drawn. Tryptase is most often used in clinical practice to support the diagnosis of anaphylaxis. There is less clinical use of histamine, due to its short plasma half-life and challenges in handling samples (Laroche et al. 1992), or of total complement, which may be affected by other conditions and also requires careful specimen handling. Abnormal results on these tests may be consistent with anaphylaxis, while normal results do not exclude the diagnosis. Acute levels should be compared with baseline levels to assist in interpretation (Golden et al. 2024).

Serum tryptase levels obtained shortly after onset of symptoms were available for three of the four anaphylactic reactions; one patient's level was slightly elevated at event onset (11.5 µg/L; upper limit of normal 10.9 µg/L) and 30 minutes later (12.6 µg/L), with no baseline for comparison, and two patients' levels were within normal limits. Plasma histamine levels were assessed in three of four reactions and were elevated in two patients: one with elevated tryptase, and one with normal tryptase. Note that normal tryptase, histamine, and/or total complement levels do not rule out anaphylaxis, and abnormal levels do not confirm the diagnosis of anaphylaxis; these are considered as contributors to the overall clinical impression. Given the available information, FDA considers these four reactions as anaphylaxis when describing risk, so that providers and patients are aware and can take appropriate risk mitigation measures.

FDA did not identify risk factors based upon medical history or concomitant medications that could predict the occurrence of anaphylaxis in patients receiving LUMISIGHT.

Table 18 summarizes AEs identified using the Hypersensitivity (Broad) FMQ and deemed related to IP by the investigator. In other words, these AEs represent those listed in Table 16, excluding the four reactions adjudicated as anaphylaxis. A summary of the limited available information is provided in Table 18, with more detailed narratives provided in section 6.4.

Table 18. Summary of 6 Preferred Terms Identified by Hypersensitivity (Broad) FMQ, Not Adjudicated by FDA as Anaphylaxis and Deemed Related to IP by the Study Investigator

Patient Identifier (Age, years)	Onset	Severity*	AE PT	Relevant Signs, Symptoms, and Laboratory Results	Action Taken	Outcome
A (62)	During injection	Moderate	Hypersensitivity	Cough, dyspnea, facial cyanosis, sternal and intercostal muscle retractions, hypoxia (SpO2 91%), hypotension, verbally responsive but sluggish, nausea. Tryptase, histamine, and total complement not measured. During needle-guided wire placement procedure 3 hours later, patient felt faint, briefly lost consciousness, and spontaneously aroused.	IP administration stopped. Treatment: oxygen by simple mask, ondansetron. Study withdrawal.	Resolved within 30 minutes
B (49)	During injection	Severe	Hypersensitivity	Dizziness, "dark spots" in vision, chest pain, numbness in hands and feet, hyperventilation, severe anxiety, elevated blood pressure, tachycardia. Tryptase and total complement not measured; histamine elevated.	IP administration stopped. Treatment: midazolam, diphenhydramine. Study withdrawal.	Resolved quickly (timing not specified)

Patient Identifier (Age, years)	Onset	Severity*	AE PT	Relevant Signs, Symptoms, and Laboratory Results	Action Taken	Outcome
C (49)	After injection	Moderate	Hypersensitivity	None reported. Tryptase, histamine, and total complement not measured.	Treatment: diphenhydramine.	Resolved on the same day
D (45)	After injection	Moderate	Rash maculopapular	Patient "presented in the OR with an allergy to Tegaderm." Tryptase, histamine, and total complement not measured.	None	Resolved after 21 days
E (57)	Unknown time on Day 1	Moderate; mild	Rash maculopapular; pruritus	Tryptase, histamine, and total complement not measured.	None	Resolved after 21 days
F (66)	Unknown time on Day 1	Moderate	Urticaria	None reported. Tryptase, histamine, and total complement not measured.	Treatment: medication (unspecified)	Resolved after 11 days

Source: FDA clinical reviewer

*Severe corresponds to investigator-assigned grade 3 severity; moderate to grade 2; mild to grade 1.

Abbreviations: AE, adverse event; IP, investigational product; PT, preferred term

Three of the six patients in Table 18 had events that resolved in 24 hours or less, while three had events that lasted multiple days (range, 11 to 21 days). A duration of >24 hours would not be consistent with anaphylaxis or an infusion-related reaction (IRR). Two reactions began during IP administration, two at an unspecified time afterwards, and two at an unspecified time that may have been before or after IP. Tryptase and total complement levels were assessed in none of these six patients, and histamine was assessed in only one, and was elevated. Based on the limited provided information, up to two of these reactions (A and B) could be consistent with non-anaphylactic, acute reactions including other immediate hypersensitivity reactions, IRRs, vasovagal presyncope, or panic attacks.

IRRs typically lack a proven immunologic mechanism, are not mediated by IgE, and yet can be clinically indistinguishable from anaphylaxis in some cases. However, there are features that, if observed, may suggest one diagnosis over the other, such as fever observed with IRR, and urticaria, repetitive cough, wheeze, throat tightness, and hypotension with anaphylaxis. The mechanism by which IRRs might occur with LUMISIGHT is less clear than with products known to yield these reactions, such as cancer therapeutics. Meanwhile, as discussed in the following paragraphs, there are known potentially allergenic moieties of LUMISIGHT, increasing the plausibility of IgE-mediated hypersensitivity reactions. Further, without a control group for comparison, it is difficult to isolate LUMISIGHT as the cause of the events, especially those that did not occur during its administration (Castells 2017).

Potential Mechanisms of Hypersensitivity Reactions

The Applicant states that the mechanism of the observed hypersensitivity reactions, including anaphylaxis, is unknown. The Applicant has hypothesized that these reactions are mast cell-mediated based on the clinical syndrome and elevation of serum tryptase and histamine in some individuals. Further, the Applicant believes that the mast cell activation is IgE-independent because these adverse events occur upon the first exposure to LUMISIGHT, without an opportunity for prior sensitization. However, as detailed in the next paragraph, FDA has identified several potentially allergenic moieties of LUMISIGHT that make it plausible that patients may indeed be sensitized prior to LUMISIGHT exposure, meaning that these reactions could be mediated by IgE. Because available data are limited, it is most accurate to consider the mechanism unknown. When considering risk mitigation, it is most appropriate to be prepared to treat these reactions as IgE-mediated, that is, with availability of emergency treatments for anaphylaxis.

FDA reviewed information provided by the Applicant, as well as the scientific literature, regarding the chemical composition, metabolites, and excipients of LUMISIGHT. There are several potential immunogenic or allergenic components of this product, including PEG-20,000, Cy5 cyanine dye, and the quencher moiety (QSY21). Polyethylene glycol (PEG) is contained in many drugs, foods, and other products and has been documented to cause hypersensitivity and anaphylaxis in rare cases (Stone et al. 2019). The Cy5 dye component has structural similarity with the approved drug indocyanine green (ICG). The ICG prescribing information contains a warning for hypersensitivity reactions and anaphylaxis. The QSY21 quencher is a xanthene dye and has limited structural similarity to the approved drug fluorescein. The fluorescein prescribing information states that rare cases of death due to anaphylaxis have been reported. Hypersensitivity and anaphylaxis to ICG and fluorescein have also been reported in the medical literature, but the mechanism of these reactions is not established (Meira et al. 2020).

Given the observed occurrence of anaphylaxis and other hypersensitivity reactions, we seek the MIDAC's opinion on potential management options for these risks. A potential approach would be to slow the rate of LUMISIGHT infusion to decrease the risk of these reactions. This approach has not been studied to evaluate its effect, if any, on clinical adverse events. FDA is not aware of adverse effects on the drug's effectiveness that would occur with a longer duration of administration. Another approach that is commonly employed in the clinical practice of medicine is administration of pre-medication to decrease the risk of infusion reactions, such as antihistamines and/or glucocorticoids. While the Applicant allowed pre-medication in their studies, this approach also has not undergone clinical evaluation for this application. The major general concern with pre-medication is potentially masking early signs of anaphylaxis, leading to delayed administration of epinephrine and poorer clinical outcomes (Shaker et al. 2020).

Because of the rate and severity of the hypersensitivity reactions observed in the clinical development program, it is necessary to consider multiple approaches to risk management, as discussed in the next section.

3.3 Risk Management

The major safety concern for LUMISIGHT is anaphylaxis and serious hypersensitivity reactions. The rate and severity of these reactions in the LUMISIGHT clinical program warrants broad considerations for risk management planning, including appropriate risk minimization strategies and postmarket assessment planning to further understand this risk.

3.3.1 Labeling

LUMISIGHT is intended to be administered to patients 2 to 6 hours before intraoperative imaging. Therefore, it is expected that patients will be in a preoperative setting where trained personnel, emergency resuscitation drugs, and equipment necessary for management of serious hypersensitivity reactions, including anaphylactic reactions, are immediately available. Nonetheless, it is important that a warning in the LUMISIGHT labeling communicate the risk of anaphylaxis and other hypersensitivity reactions and the need to monitor patients and to have appropriate personnel, medications, and equipment available (Figure 8). To increase awareness of the risk, a boxed warning is also planned (Figure 9).

Figure 8. Proposed Language for the Warnings and Precautions Section of LUMISIGHT Prescribing Information

5.1 Anaphylaxis and Serious Hypersensitivity Reactions

Prepare for the possibility of drug hypersensitivity reactions (including anaphylactic reactions), which can occur during or following administration, and take the necessary precautions.

In clinical studies, 4 of 726 (0.6%) patients treated with LUMISIGHT experienced signs and symptoms consistent with anaphylaxis. Signs and symptoms associated with hypersensitivity reactions included anxiety, chest pain, cyanosis, dizziness, dyspnea, erythema, headache, hypoesthesia, hypotension, hyperventilation, lip swelling, maculopapular rash, nausea, paresthesia, pruritus, urticaria, visual changes, and vomiting *[see Adverse Reactions (6.1)]*.

Before LUMISIGHT administration, assess all patients for any history of hypersensitivity reaction to contrast media or products containing polyethylene glycol (PEG), as these patients may have an increased risk for hypersensitivity reaction to LUMISIGHT. In clinical studies, 3 out of 4 patients that experienced anaphylaxis did not have a history of hypersensitivity reaction to contrast media or products containing PEG.

Always have emergency resuscitation drugs, equipment, and trained personnel available. Monitor all patients for hypersensitivity reactions using symptom reporting, direct observation, and vital sign measurements. If a hypersensitivity reaction is suspected, immediately discontinue the injection and initiate appropriate therapy. LUMISIGHT is contraindicated in patients with a history of hypersensitivity reaction to pegulicianine *[see Contraindications (4)].*

Figure 9. Proposed Boxed Warning for LUMISIGHT

WARNING: ANAPHYLAXIS AND SERIOUS HYPERSENSITIVITY REACTIONS

Serious hypersensitivity reactions, including anaphylaxis, can occur during or following administration of LUMISIGHT. Anaphylaxis occurred in 4/726 (0.6%) of patients in clinical studies. Signs and symptoms associated with other hypersensitivity reactions included anxiety, chest pain, cyanosis, dizziness, dyspnea, erythema, headache, hypoesthesia, hypotension, hyperventilation, lip swelling, maculopapular rash, nausea, paresthesia, pruritus, urticaria, visual changes, and vomiting.

- **Before LUMISIGHT administration, assess all patients for any history of hypersensitivity reaction to contrast media or products containing polyethylene glycol (PEG).**
- **Always have emergency resuscitation drugs, equipment, and trained personnel promptly available.**
- **Monitor all patients for hypersensitivity reactions. If a hypersensitivity reaction is suspected, immediately discontinue the injection and initiate appropriate therapy.**
- **LUMISIGHT is contraindicated in patients with a history of hypersensitivity reactions to peguliciane *[see Warnings and Precautions (5.1)].***

Among the six most significant adverse events (hypersensitivity SAEs and AEs leading to discontinuation), initial symptoms were reported during the injection of LUMISIGHT in five patients (83%) and immediately after the injection in one patient. This group includes all of the reactions graded

as severe or life threatening. These results support the feasibility of monitoring for hypersensitivity reactions as a risk mitigation strategy, as the most intense patient monitoring will likely be during and shortly after LUMISIGHT administration. If Lumisight is approved, and used in a larger population, there may be a wider variety of reactions with varying severity and time to onset.

Patients with a history of anaphylaxis to polyethylene glycol (PEG) or a history of anaphylaxis to contrast agents have been excluded from LUMISIGHT studies beginning early in development. After the initial report of anaphylaxis, the Applicant amended clinical study protocols to exclude patients with history of allergic reactions (of any severity) to contrast agents. In part, this was due to the history of hives after iodinated contrast in a patient who experienced anaphylaxis related to LUMISIGHT. Anaphylaxis and other hypersensitivity reactions continued to occur, and there are insufficient data to determine whether the exclusion criteria lowered the incidence. However, we agree with the Applicant that it is possible that patients with hypersensitivity to contrast media or PEG might have increased risk of reaction after LUMISIGHT, and it is reasonable to assess patients for history of these reactions. Similarly, it is reasonable to contraindicate use of LUMISIGHT in patients with history of hypersensitivity reaction to LUMISIGHT due to the potential for recurrent hypersensitivity reaction.

While it would not directly alter the risk of hypersensitivity, restriction of the indicated population to those with higher risk of having positive margins after standard of care lumpectomy could potentially improve the benefit-risk balance. However, this strategy would require defining patients with higher risks of positive margins. Critically, it would also likely require additional studies, as it is not clear that effectiveness could be extrapolated from the population studied in the existing clinical trials.

3.3.2 Risk Evaluation and Mitigation Strategies (REMS)

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require applicants or application holders to develop and comply with a risk evaluation and mitigation strategies (REMS) for a drug if the Agency determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond labeling. The elements of a REMS can include: Medication Guide or patient package insert, a communication plan for healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, elements to assure safe use (ETASU), and an implementation system. All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared and submitted by the application holder and reviewed by FDA.

ETASU can include one or more of the following:

1. Health care providers who prescribe the drug have particular training or experience, or are specially certified
2. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
3. The drug be dispensed to patients only in certain health care settings, such as hospitals
4. The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
5. Each patient using the drug be subject to monitoring
6. Each patient using the drug be enrolled in a registry

ETASU can impose significant burdens on the healthcare system and potentially impact patient access to treatment; therefore, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

Because patients can receive LUMISIGHT up to 6 hours prior to imaging and surgery, there may be variability in how patients are monitored after administration. The protocols for studies CL0006, CL0007, and CLP0008 did not provide specific monitoring procedures, but they stated that patients should be observed after the administration of LUMISIGHT with standard preoperative, intraoperative, and postoperative monitoring.

If it is determined that additional risk mitigation strategies beyond labeling are necessary to ensure that the benefits of LUMISIGHT outweigh the risk of anaphylaxis, a REMS can restrict distribution of LUMISIGHT to healthcare settings that are certified in the REMS. The certified healthcare settings may be required to develop policies and procedures that support monitoring as defined by the prescribing information, so that anaphylaxis is recognized early and appropriate intervention and treatment can be administered promptly. If there is a concern regarding delayed anaphylaxis, the REMS can include that patients are informed about the risk of anaphylaxis, symptoms of anaphylaxis, and the need to call emergency services. At this time, the Applicant has not submitted a proposed REMS.

3.4 Postmarket Assessment Planning

To better understand the risk, the FDA may require a postmarketing safety study that measures rates of anaphylaxis and other hypersensitivity reactions. Such a study may provide incidence estimates to inform future assessments of this risk and the risk mitigation strategy. If adequately designed and executed, this postmarketing safety study may also provide data to further characterize the risk of anaphylaxis and hypersensitivity reactions.

Enhanced pharmacovigilance for hypersensitivity reactions, including anaphylaxis, represents a potential risk assessment approach. This may involve FDA requesting the Applicant to summarize and assess interval and cumulative data for adverse events of interest (e.g., hypersensitivity reactions) at a recurring frequency defined by FDA. FDA may also request that the Applicant submit expedited 15-day individual case safety reports for certain labeled adverse events of interest. Enhanced pharmacovigilance would not directly reduce the risk of hypersensitivity, but would foster more timely submission of hypersensitivity related safety information to FDA and may allow for a more rapid regulatory response if the observed reporting frequency, time to onset, or clinical severity of hypersensitivity reactions is greater than expected.

4 Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This pre-decisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	• Breast cancer is a life threatening and debilitating disease and is the most common cancer in American females. • Most women diagnosed with stage 0, I, or II breast cancer have the option of receiving either mastectomy or breast conserving surgery (BCS) followed by adjuvant radiotherapy. Five-year survival is >99% for patients with stage I disease and 93% for patients with stage II disease. • Randomized clinical trials have reported equivalent survival outcomes between mastectomy or BCS plus adjuvant radiotherapy. • A positive margin after BCS indicates incomplete tumor resection and is one of the primary prognostic factors for same-side breast tumor recurrence, even if re-excision is performed. • Local radiotherapy boost or systemic therapy have not been shown to eliminate the excess risk of same-side tumor recurrence after BCS with positive margins. Therefore, patients typically receive re-excision surgery to address positive margins. • Re-excision is associated with added risk of surgical and anesthetic complications, patient distress, surgical pain, and delay of the start of adjuvant radiotherapy; it may also increase the risk of poor cosmetic outcomes.	• Breast cancer is a serious condition, representing the second most common cause of cancer-related death in American females, although fatalities are primarily among patients with stage III or IV disease. • BCS is commonly offered to patients with stage 0-II breast cancer. • When performing BCS, the main objective is to obtain tumor-negative resection margins while maintaining the cosmetic appearance of the breast. • A second surgery to address positive margins after the first BCS is associated with increased recurrence and re-excision risks.
Current Treatment Options	• Histopathology assessment of permanent sections from excised tissue to determine margin status is standard of care, however results are not available during surgery. Positive margin rates are approximately 20-40%. • Intra-operative approaches to margin assessment are available but have drawbacks: – Frozen section or touch prep histopathology analysis	• Because standard of care histopathology determination of margin status is not made until after completion of surgery, addressing positive margins typically requires additional surgery. • Assessing margins during BCS presents the potential to reduce the number of patients who have positive margins after the first surgery.

	Evidence and Uncertainties	Comments to the Advisory Committee
	can provide results during BCS and are obtained in addition to permanent section analysis by some surgeons, but the sensitivity is suboptimal. – Specimen radiography can be performed during BCS to assess for potential incomplete resection, but this approach is limited to patients who have a mammographic finding such as calcifications, and it cannot fully assess margin status. – Radiofrequency spectroscopy utilizes electromagnetic scattering, reflectance, and absorbance properties from tissue to assess for the presence of tumor at the margin of excised specimens during BCS. However, the sensitivity is suboptimal. • Some surgeons elect to remove a thin rim of tissue from all surfaces of the resection cavity after completing a lumpectomy (termed comprehensive shaves). This approach is reported to reduce the positive margin rate by up to 50 percent.	• Currently available techniques for intraoperative margin assessment have limitations (e.g., suboptimal sensitivity) and no FDA-approved products are available to aid examination of the lumpectomy cavity for cancer after the main specimen is removed in standard of care BCS. • A method that can detect cancer in the resection cavity during BCS after main specimen excision is expected to allow removal of additional cancer compared to BCS alone.
Benefits	• The Applicant conducted one adequate and well-controlled trial of LUMISIGHT, CL0007. Confirmatory evidence of effectiveness was provided by an additional Applicant-conducted trial, CL0006. • In CL0007, 27 of 357 (7.6%) patients had cancer confirmed by histopathology in at least one LUMISIGHT-guided shave taken after completion of SoC lumpectomy. The tissue-level sensitivity and specificity were 49.1% and 86.5%, respectively. • Overall, 17.4% of patients had positive margins following standard of care surgery. Among these 62 patients, 14.5% converted to negative margins following LUMISIGHT-guided surgery (overall conversion rate 2.5%). Eight of these nine patients had no cancer removed in the LUMISIGHT-directed shave. However, these eight patients would have been considered for a second surgery if LUMISIGHT had not been used. • Among patients with no LUMISIGHT-guided shaves, the scaled patient satisfaction score on the BREAST-Q at 6 months post-surgery was 75.4 versus 71.0 for patients with at least one LUMISIGHT-guided shave. A similar difference in scores was	• Diagnostic performance was assessed by tissue-level sensitivity and specificity. Tissue-level specificity met the predefined success threshold of 60%. Sensitivity did not meet the predefined success threshold of 40% at the lower bound of the 95% confidence interval. However, this threshold was not set based on the lowest clinically useful value, and the co-primary endpoint of cancer removal in a LUMISIGHT-guided shave met its threshold. The combined sensitivity and specificity results indicate adequate performance for imaging cancer in the lumpectomy cavity. • While margin conversion rate was not a primary endpoint in CL0007, it is important to consider because patients who convert are most likely to benefit from the product, through elimination of second surgeries. As most patients who converted did not have cancer removed in a LUMISIGHT-directed shave and the number of

	Evidence and Uncertainties	Comments to the Advisory Committee
	seen at baseline. However, only 45% of the trial participants completed the survey at baseline and only 14% at 6 months.	false positive tissues was high, there is uncertainty regarding the fraction of converters who benefited from the product.
Risks and Risk Management	• The major safety concern of LUMISIGHT is hypersensitivity. • Overall, hypersensitivity reactions occurred in 4.8% of patients. • Hypersensitivity reactions judged by the investigator to be related to LUMISIGHT occurred in 1.4% of patients, including 4 cases of anaphylaxis (0.6%). • All cases of anaphylaxis occurred during or immediately after the administration. • Limited information is available on how patients were monitored following the administration of LUMISIGHT in the clinical trial. • The Applicant has proposed that patients should be monitored for 15 minutes following the administration of LUMISIGHT. • False positive and false negative rates of LUMISIGHT should also be considered. Overall, 43.4% of patients had at least one false positive tissue and 7.8% had at least one false negative tissue.	• The incidence of anaphylaxis is concerning in a product intended to be used in an older population with potential comorbidities. • LUMISIGHT will be administered as a single dose in a pre-operative, highly controlled setting. • Availability of immediate access to emergency treatment for the entirety of the 2 to 6 hour preoperative period is recommended as serious hypersensitivity reactions could occur at any time. • Multiple risk management and postmarket assessment strategies for hypersensitivity and anaphylaxis are under consideration (e.g., boxed warning, postmarketing studies, REMS, enhanced pharmacovigilance).

Summary of Benefit-Risk

For a drug to be approved for marketing in the United States, FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. A benefit-risk assessment for the LUMISIGHT and Lumicell DVS combination product requires careful consideration of the evidence and remaining uncertainties about its key benefits (as demonstrated in the development program) and potential risks, as well as the ability to mitigate such risks. This assessment should consider the unmet need for patients with breast cancer who are undergoing breast conserving surgery, while bearing in mind the likelihood that most patients will receive a single dose in their lifetime.

The pivotal trial for LUMISIGHT demonstrated modest diagnostic performance for detection of cancer in the resection cavity after standard of care breast conserving therapy. However, detection of cancer in this setting may not necessarily translate into patient benefit. There is some uncertainty regarding the magnitude of effect for secondary endpoints that are more directly correlated with benefit.

The main risk to be set against the benefits of LUMISIGHT is the risk of anaphylaxis and serious hypersensitivity reactions. Because the drug will be administered in the preoperative setting, labeling to ensure providers are aware of the need to monitor patients for reactions and maintain availability of trained personnel and resuscitation drugs and equipment is a key risk mitigation strategy. Additional risk mitigation strategies are under consideration.

	Evidence and Uncertainties	Comments to the Advisory Committee
Based on the clinical trial data, two key questions are important to consider for this product's benefit-risk assessment. First, do the clinical benefits of this product outweigh the risk of anaphylaxis and severe hypersensitivity reactions? Second, if so, what risk mitigation strategies are necessary to achieve a positive benefit-risk balance?		

Table 19. Benefit-Risk Effects Table

Outcome	Measures	Point Estimate [95% CI]	Uncertainties & Strength of Evidence
	Benefit Assessment		
Intra-operative detection of residual breast cancer tissue following SoC BCS	• Tissue-level sensitivity[a] (n=69) • Tissue-level specificity[a] (n=2277) • Patient-level detection of cancer in a therapeutic shave[a] (n=357)	• 49.1% [36.4%, 61.9%] • 86.5% [84.5%, 88.3%] • 7.6% [5.0%, 10.8%]	LUMISIGHT met the prespecified success threshold for specificity but did not meet the threshold for sensitivity.
Avoidance of second surgery	• Percentage of patients who have positive margins after SOC surgery in the mITT population (n=357) • Percentage of patients who have positive margins after LUMISIGHT-guided surgery (n=357) • Patient-level conversion rate from positive to negative margins among patients with positive margins after SOC surgery (n=62)[b,c] • Patient-level conversion rate in the mITT population (n=357)[b,c] • Percentage of patients with cancer removed in a LUMISIGHT-guided shave among patients who converted (n=9)	• 17.4% [13.4%, 21.3%] • 15.4% [11.7%, 19.2%] • 14.5% [5.8%, 23.3%] • 2.5% [0.9%, 4.1%] • 11.1% [0.3%, 48.2%]	Few patients who converted from positive margins after SoC surgery to negative margins after LUMISIGHT-guided surgery had cancer in a LUMISIGHT-directed shave, raising uncertainty regarding the attribution to the product.

Outcome	Measures	Point Estimate [95% CI]	Uncertainties & Strength of Evidence
Patient Satisfaction	Scaled patient satisfaction score, range 0 to 100, (BREAST-Q) at baseline in patients with: • No LUMISIGHT-directed shaves • At least 1 LUMISIGHT-directed shave	 • 64.1 [58.7, 69.5] • 61.3 [56.5, 66.2]	At baseline, 45% (161/357) of patients completed the patient satisfaction survey. Only 14% (50/357) completed the survey at 6 months.
	Scaled patient satisfaction score range 0 to 100 (BREAST-Q) at 6 months post-surgery in patients with: • No LUMISIGHT-directed shaves • At least 1 LUMISIGHT-directed shave	 • 75.4 [63.5, 87.4] • 71.0 [62.7, 79.4]	
Risk Assessment			
Intra-operative misclassification of residual breast cancer tissue following SoC BCS	• Patients with at least 1 false positive tissue (n=357)[c] • Patients with at least 1 false negative tissue (n=357)[c]	• 43.4% [38.3%, 48.6%] • 7.8% [5.1%, 10.6%]	High false positive and false negative rates increase the risk of misdiagnosis.
Hypersensitivity reactions	• Overall hypersensitivity incidence (n=726) • Investigator-judged LUMISIGHT-related hypersensitivity incidence (n=726) • Anaphylaxis incidence (n=726)	• 4.8% [3.4%, 6.6%] • 1.4% [0.7%, 2.5%] • 0.6% [0.2%, 1.4%]	The lack of an unexposed concurrent control group in the setting of pre-operative confounders introduces complexities in the attribution of hypersensitivity events to LUMISIGHT.

Source:
[a] Primary endpoint; [b] Secondary endpoint; [c] via normal approximation
Abbreviations: BCS, breast-conserving surgery; PM, positive margin; SoC, standard of care

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6 Appendix

6.1 LUMISIGHT and Lumicell DVS Background

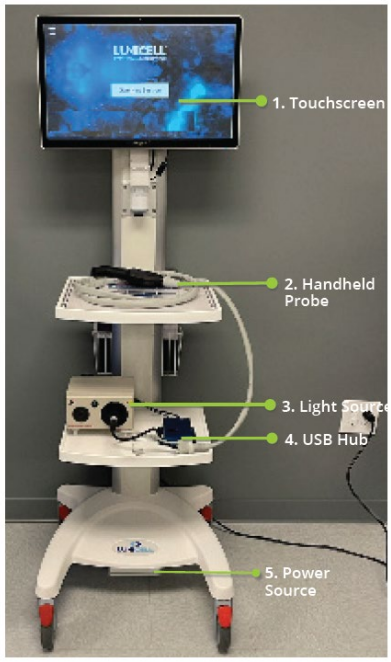
6.1.1 LUMISIGHT and the Lumicell Direct Visualization System Combination Product Description

The combination product consists of an optical imaging agent, LUMISIGHT (pegulicianine) for injection (NDA 214511), and a fluorescence imaging device with a proprietary system software, the Lumicell Direct Visualization System (Lumicell DVS; P230014). LUMISIGHT is administered to the patient at the hospital via intravenous injection 2 to 6 hours prior to imaging. After removal of the main lumpectomy specimen, the Lumicell DVS is used to scan the lumpectomy cavity for fluorescence from activated LUMISIGHT. The Lumicell DVS consists of a cart-mounted computer console and a handheld probe attached to a light source with an optical fiber cable, which is used to excite LUMISIGHT and capture real-time fluorescence images with a camera. The data are analyzed in real-time via Lumicell's proprietary Patient Calibrated Tumor Detection Software to highlight regions within the lumpectomy cavity that are suspicious of containing residual cancer to assist in their removal.

6.1.2 Lumicell Direct Visualization System (DVS) Description

The Lumicell DVS (Figure 10) consists of a workstation and a handheld probe. The handheld probe connects to the workstation's light source via an optical fiber cable. These components are used together to excite the optical imaging agent, LUMISIGHT, and capture and display real-time fluorescence images. During surgery, the handheld probe is used to scan the lumpectomy cavity for activated LUMISIGHT by delivering 630±5 nm excitation light and measuring the fluorescence emission signal using a camera after filtering through a 662.5 to 737.5 nm bandpass filter. The resulting data are transferred to the workstation's touchscreen via USB cable. The data are analyzed in real-time via Lumicell's proprietary Patient Calibrated Tumor Detection Software to highlight regions within the lumpectomy cavity that are suspicious of containing residual cancer.

Figure 10. Diagram of the Lumicell DVS



Source: Figure 1 of Lumicell Direct Visualization System Instructions for Use.
Abbreviation: DVS, direct visualization system

Pegulicianine Imaging Agent

Lumicell engineered pegulicianine, a fluorescence-based imaging agent that accumulates within and around cells. In regions enriched with cathepsin enzymes, such as cancer cells, pegulicianine is altered to fluoresce when illuminated with 649 nm light. In its intact state, the fluorescence of pegulicianine is suppressed by an internal quencher molecule (QSY21). The presence of cathepsin enzymes is not fully confined to cancer cells. Once cathepsin enzymes cleave pegulicianine at its amino acid backbone, the quencher is released and the fluorescent dye (Cy5) in pegulicianine emits detectable fluorescence when it absorbs red light.

Product, Dose, and Mode of Administration

LUMISIGHT for injection is administered intravenously over 3 minutes, 2 to 6 hours prior to the lumpectomy procedure at a dose of 1 mg/kg.

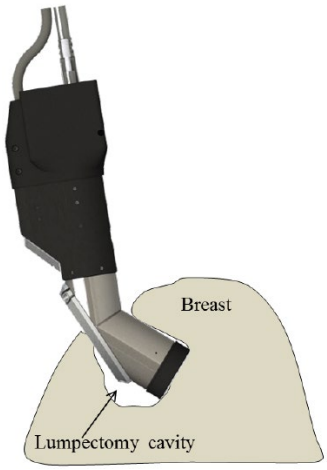
Lumicell DVS

The Lumicell DVS consists of a computer control unit, monitor, and light source mounted on a cart and a hand-held optical head (LUM002/LUM003). The computer control unit collects, analyzes (based upon Lumicell's detection algorithm), and displays the resulting images gathered by the imaging head in real-time. The light source provides the illumination to excite the fluorescent dye present in LUMISIGHT. Light is transferred from the light source to the imaging head using an optical fiber bundle. The imaging head (Figure 11) was designed as a lightweight hand-held tool with a small profile to allow easy maneuverability and limited intrusiveness in the operating room. Because incisions and lumpectomy cavities can vary in size, Lumicell offers two options for the distal end diameter: LUM002, which has a 2.6 cm field of view and a 3.1 cm outer diameter and LUM003, which has a 1.3 cm field of view and a 1.9

cm outer diameter. The surgeons will be able to choose which device size to use for any given surgery. These two device options were proven to be optically equivalent when imaging freshly excised breast tissue. Both imaging heads have a 45° bend at the distal end for examination of the walls of the lumpectomy cavity.

The hand-held imaging head will be used within the sterile surgical field. Consequently, a sterile barrier assembly will be provided to cover the imaging head, which comes into contact with both the surgeon and the patient's exposed tumor bed. The sterile barrier assembly is installed on the imaging head in the OR using sterile procedures.

Figure 11. Diagram of the Lumicell DVS Imaging Head



Source: Figure 2 of CL0007 Protocol.
Abbreviation: DVS, direct visualization system

Surgeon and Site Personnel Commercial Training

All surgeons are required to undergo training and complete a modified proficiency program before device use.

A program is designed to describe the process for training users (surgeons and clinical site personnel) on the use of the Lumicell Direct Visualization System (DVS). It is a requirement for surgeons to receive this training program before receiving login credentials to use the Lumicell DVS. This procedure is not required for surgical support staff or sterile processing technicians, however, Lumicell will offer training to these user groups upon request.

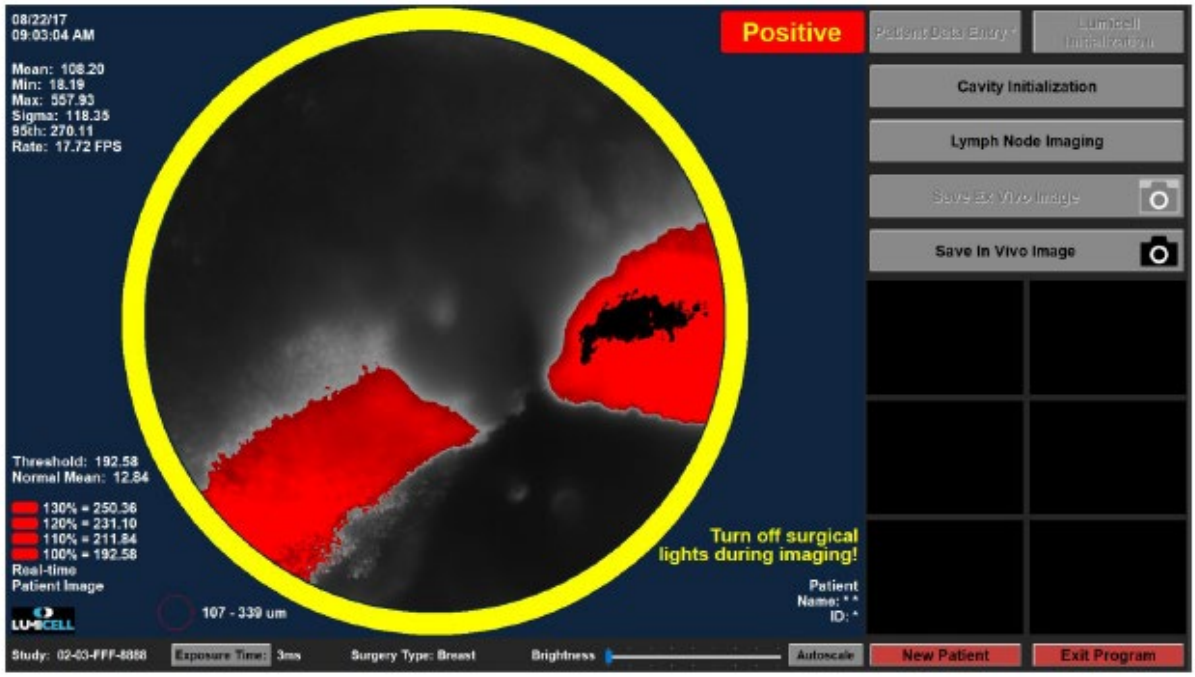
It is the responsibility of Lumicell's field personnel to oversee the execution of this procedure. It is the responsibility of Lumicell's quality department to assist in the execution of this procedure and ensure that updates to the human factors validation or usability risk assessment are reflected in appropriate documentation. The training materials include Lumicell DVS Instructions for Use, Surgical Technique Guide, Equivalency Study Wide-field Phantom Generation Procedure, Reprocessing Instructional Poster, Startup Guide, Lumicell DVS User Training Videos, Administrative Resource Guidance, and Surgeon and Site Personnel Training Record.

LUM Decision Software

The LUM Imaging System is powered by Lumicell's proprietary decision software. The decision software uses an initial set of images acquired from the lumpectomy cavity after the main specimen is removed to set the tumor detection threshold.

While the surgeon scans the lumpectomy cavity walls with the imaging head, the decision software compares the intensity of an image against the tumor detection threshold and identifies whether a region of the image is suspected to contain tumor. Regions with fluorescence signal above the threshold are highlighted in the computer monitor for the surgeon to see in real-time; that is, there is no delay between the scanning of a region and the display of the results from that region. Figure 12 shows the user interface and what the surgeon sees during scanning of the cavity walls.

Figure 12. Sample Image from the LUM Decision Software



Source: Figure 3 of CL0007 Protocol.

6.2 LUMISIGHT and Lumicell DVS Combination Product Principles of Operation

The active ingredient in 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 the intact state (as manufactured), the dark quencher absorbs fluorescence emitted by the fluorophore, rendering the molecule fluorescently inactive. LUMISIGHT is administered to patients undergoing breast conserving surgery 2 to 6 hours prior to the first image recorded. LUMISIGHT then accumulates preferentially in tumors and surrounding tissues, producing a fluorescent signal after its peptide backbone is cleaved by proteases, such as cathepsins, that are overexpressed by tumors. 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, without the PEG 20,000 (Whitley et al. 2016).

Upon enzymatic activation, the fluorescent fragments can be detected by the Lumicell DVS. During surgery, the device with a handheld probe is used to collect photons emitted by activated LUMISIGHT in the tumor bed (Smith et al. 2018; Smith et al. 2020; Lanahan et al. 2021; Hwang et al. 2022). The device works by exciting the fluorophore component of LUMISIGHT using the output of a light-emitting diode (LED) with a peak wavelength of 630±5 nm and collecting the fluorescence emission of the dye through a 662.5 to 737.5 nm bandpass filter and directing the signal to a camera located within the probe.

Lumicell's proprietary patient calibrated tumor detection software analyzes the images and displays them on a computer screen in real-time. Tissue identified as suspicious by the software is color-coded red on the screen for ease of identification and to guide the surgeon for its removal.

Main Specimen Resection

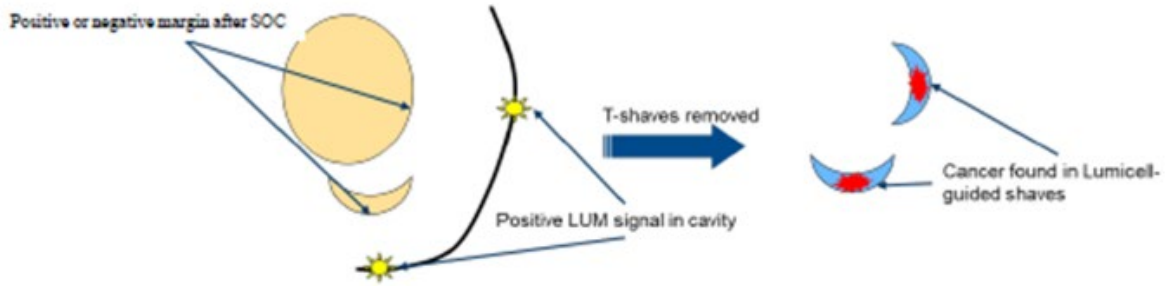
The surgeon shall remove the main specimen per standard of care with the intention of achieving grossly negative margins.

Lumicell Procedure

After the standard of care is completed (standard of care may include comprehensive shaves or selective shaves based on palpation of the main specimen or cavity walls, X-ray imaging of the intact main specimen, intraoperative frozen section pathology, or visual examination), the surgeon will scan the tumor bed to collect images of the cavity walls and remove therapeutic shaves as indicated by the LUM decision software anytime the LUM Imaging System indicates signal above the threshold (LUM positive signal shown in red in the computer screen). The software will automatically turn on the tumor detection algorithm to allow visualization and navigation of the lumpectomy cavity with highlighting of suspected tumor by the tumor detection algorithm.

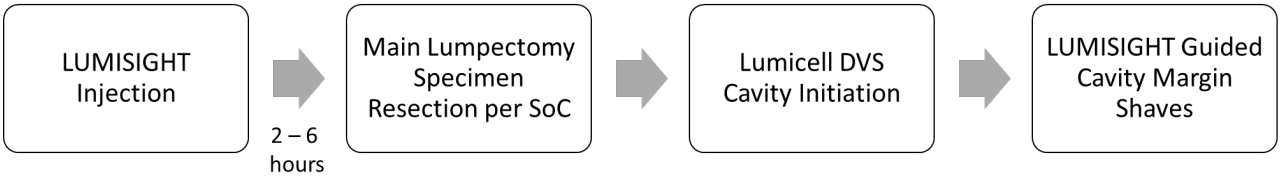
Figure 13 and Figure 14 show diagrams of the intended operation.

Figure 13. Diagram of Removal of Residual Cancer in LUMISIGHT-Guided Surgery



Source: Figure 9-6 of CL0006 Clinical Study Report.
Abbreviations: LUM, LUMISIGHT; SoC, standard of care; T-shaves therapeutic shaves

Figure 14. Surgical Work Flow



Source: Adapted from Figure 1 of CL0007 Clinical Study Report.
Abbreviations: DVS, direct visualization system; SoC, standard of care

6.3 FDA Adjudication of Anaphylaxis

NIAID/FAAN 2006 Criterion 1 (Sampson et al. 2006) for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when [the following criterion is] fulfilled:

7. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

6.4 Adverse Event Narrative Summaries

Narrative Summaries of Four Events Adjudicated by FDA as Anaphylaxis

Patient 1: Anaphylactic reaction

A 73-year-old white female with DCIS of the left breast and a history of urticaria with IV and PO iodinated contrast was scheduled to receive 104 mg (1 mg/kg) LUMISIGHT over a 3-minute IV push. Two minutes into the injection (30 mg in 3 mL administered), the patient reported chest tightness and shortness of breath. Staff noted flushing of her face and upper body and stopped the injection. The patient was noted to be diaphoretic, nauseated, and having trouble breathing. She then became briefly apneic and cyanotic, with palpable pulses and a generalized rash.

Emergent treatment consisted of one minute of assisted ventilation with 10 liters of oxygen via a bag-mask. In addition, epinephrine 0.2 mg IV, methylprednisolone IV, and IV fluid boluses were given. Diphenhydramine IV was administered and more epinephrine (0.4 mg IV, followed by 0.2 mg IV) was administered. Hypotension was noted. A continuous epinephrine infusion was started at 2 mg/min. The patient was transferred to the intensive care unit. She recovered quickly and was weaned from the epinephrine drip within 90 minutes. Blood was not collected to assess tryptase, histamine, or total complement levels. The patient was discharged home the following day.

This event narrative meets clinical criteria for anaphylaxis as the patient had flushing, rash, respiratory distress, and hypotension while receiving LUMISIGHT. The patient had a history of urticaria with iodinated contrast agents. She required epinephrine (several doses and infusion), bag-mask assisted ventilation, and ICU admission for recovery.

Patient 2: Anaphylactic reaction (PT hypersensitivity)

A 47-year-old white female with IDC and DCIS of the left breast and no prior history of drug allergy received an unspecified nuclear medicine injection and underwent wire placement in anticipation of breast surgery. Approximately 1.25 hours later, administration of 61 mg (1 mg/kg) LUMISIGHT as a 3-minute IV push was initiated. Two minutes into the injection (27 mg in 2.7 mL administered), the patient had nausea and vomiting, and IP administration was stopped. The patient's blood pressure was 66/33 mmHg (baseline 113/76 mmHg) and heart rate was 54 bpm (the same as baseline). She had generalized erythema without discrete rash. A pulmonary exam was negative for wheezing and stridor, and oxygen saturation remained at 100% on room air. She was placed in reverse Trendelenburg and given IV fluids, diphenhydramine IV, and ondansetron. By 25 minutes after symptom onset, the patient fully recovered. Serum tryptase level was elevated at event onset (11.5 µg/L, normal range ≤10.9 µg/L) and 30 minutes later (12.6 µg/L); baseline level was not available for comparison. Plasma histamine levels were elevated at event onset (52 nmol/L, normal range 0 to 8 nmol/L) and 30 minutes later (22 nmol/L). Total complement level was normal.

This event narrative meets clinical criteria for anaphylaxis as the patient experienced erythema and hypotension while receiving LUMISIGHT. The patient had no history of drug allergy. The diagnosis of anaphylaxis is supported by elevated tryptase and histamine levels, although baseline levels were not available to aid in interpretation. Although the patient received an unspecified nuclear medicine injection (presumably Tc 99m sulfur colloid or Tc 99m tilmanocept as specified in the clinical study protocol), since the reaction occurred 1.25 hours after the nuclear medicine, but during LUMISIGHT administration, LUMISIGHT is the most likely cause of the suspected anaphylaxis.

Patient 3: Anaphylactic reaction

A 40-year-old white female with DCIS of the left breast and no prior history of drug allergy was scheduled to receive 91 mg (1 mg/kg) LUMISIGHT over a 3-minute IV push. One minute into the injection (22 mg in 2.2 mL administered), the patient reported shortness of breath, swollen lips, tingling in the tongue, hands, and feet, eye redness, black spots in vision, nausea, and vomiting. IP administration was stopped. The patient's blood pressure was 110/89 mmHg, and heart rate was 88 bpm. She was treated with diphenhydramine IV, hydrocortisone IV, ondansetron IV, and famotidine IV. After 20 to 30 minutes, the patient recovered, except for tingling of the feet, which took 2 hours to resolve. Serum tryptase levels obtained at event onset and 30 minutes later were normal. Plasma histamine levels were elevated at event onset (55 nmol/L, normal range 0 to 8 nmol/L) and 30 minutes later (11 nmol/L). Total complement level was normal.

This event narrative meets clinical criteria for anaphylaxis as the patient had lip angioedema and shortness of breath while receiving LUMISIGHT. She had no history of drug allergy. Plasma histamine levels were elevated. She received antihistamine and glucocorticoid treatment but did not receive epinephrine, and she recovered within 30 minutes of symptom onset.

Patient 4: Anaphylactic reaction

A 61-year-old white female with IDC of the left breast and no prior history of drug allergy received 61 mg (6.1 mL, 1 mg/kg) LUMISIGHT over a 3-minute IV push. At the completion of the infusion, the patient reported itching and numbness of the hands, feet, and lips. No shortness of breath or rash was observed. The patient's blood pressure was 64/38 mmHg, and heart rate was 65 bpm during the event

(baseline 131/84 mmHg and 54 bpm). She was placed in reverse Trendelenburg and given IV fluids. She recovered within 30 minutes. Tryptase, histamine, and total complement levels obtained at 30 minutes and 60 minutes after event onset were normal. It was noted in the narrative that vasovagal reaction could not be ruled out.

Three hours later after pre-surgical wire placement, the patient reported feeling light-headed and seeing bright lights. She was given ephedrine and placed supine. She recovered and underwent lumpectomy as planned.

The initial event narrative meets clinical criteria for anaphylaxis as the patient experienced itching and hypotension immediately upon completion of LUMISIGHT administration. The patient had no history of drug allergy. She was treated with IV fluids and positioning. Although the second episode may be consistent with a vasovagal reaction, the initial event is adjudicated as anaphylaxis.

Narrative Summaries of Six Events Identified by Hypersensitivity (Broad) FMQ, Not Adjudicated by FDA as Anaphylaxis and Judged Related to IP by the Study Investigator

Patient A: Moderate hypersensitivity

A 62-year-old white female with IDC of the right breast and no prior history of drug allergy was scheduled to receive 85 mg (1 mg/kg) LUMISIGHT over a 3-minute IV push. Two minutes into the injection (45 mg in 4.5 mL administered), the patient coughed once and had difficulty breathing, with rapid worsening. IP administration was stopped. Facial cyanosis and sternal and intercostal muscle retractions were noted. She was given 8 L/minute of oxygen by simple mask. Nine minutes after starting the injection, her oxygen saturation was 91% and blood pressure was 90/50 mmHg (baseline 134/82 mmHg) with heart rate of 88 bpm. She was verbally responsive but sluggish. By 24 minutes after the injection, oxygen saturation (98%), blood pressure (96/61 mmHg), heart rate (83 bpm), and respiratory rate (16 breaths/minute) improved. She was alert, conversing with staff, and in no distress. It was noted that she had a “rapid return of spontaneous respirations,” although the exact time of return was not documented. The patient then reported nausea, and ondansetron IV was administered. Clinical laboratory assessments and ECG performed at approximately 1.5 hours were unremarkable; tryptase, histamine, and total complement were not assessed.

During needle-guided wire placement procedure 3 hours after LUMISIGHT administration, the patient felt faint, briefly lost consciousness, and spontaneously aroused. After recovering, she completed surgery. She withdrew from the study.

This event narrative does not meet clinical criteria for anaphylaxis due to the lack of cutaneous or mucosal involvement. It is notable that the patient had a syncopal episode the same day during a presurgical procedure.

Patient B: Severe hypersensitivity

A 49-year-old white female with IDC of the left breast and history of allergies to cefaclor (anaphylaxis) and walnut (tongue swelling) was scheduled to receive 124 mg (1 mg/kg) LUMISIGHT over a 3-minute IV push. One minute into the injection (64 mg in 6.4 mL administered), she reported dizziness and “dark spots” in her vision. IP administration was stopped. The patient reported chest pain and numbness in her hands and feet. Hyperventilation and severe anxiety were noted. Her blood pressure was elevated at 196/96 mmHg, and her heart rate was 141 bpm (157/98 mmHg and 100 bpm at baseline). She was

treated with midazolam and diphenhydramine. The patient recovered quickly (timing not specified), underwent surgery, and was discharged home. Tryptase and total complement were not assessed. Histamine was elevated (22 nmol/L) and remained elevated (12 nmol/L) 30 minutes later. She withdrew from the study.

This event narrative does not meet clinical criteria for anaphylaxis due to the lack of cutaneous or mucosal involvement. However, plasma histamine was elevated, while tryptase was not assessed. The patient had a history of drug and food allergies.

Patient C: Moderate hypersensitivity

A 49-year-old white female with ILC of the left breast received 82 mg (1 mg/kg) LUMISIGHT. An unspecified time after IP administration was completed, she experienced unspecified symptoms reported as the verbatim term “allergic reaction” and was treated with diphenhydramine. Symptoms resolved in less than 24 hours, and she proceeded with surgery. Tryptase, histamine, and total complement were not assessed.

Based on the limited information provided, this event does not meet criteria for anaphylaxis.

Patient D: Moderate rash maculopapular

A 45-year-old female with IDC and DCIS of the left breast and history of allergies to Tegaderm and chlorhexidine gluconate received 54 mg (1 mg/kg) LUMISIGHT. An unspecified time after IP administration was completed, she “presented in the OR with an allergy to Tegaderm.” The AE was reported as the verbatim term “rash maculopapular.” No action was taken, and the AE duration was 21 days. Tryptase, histamine, and total complement were not assessed.

Based on the limited information provided, this event does not meet criteria for anaphylaxis, as this was a skin-limited reaction. The duration of 21 days is not consistent with anaphylaxis. Based upon the narrative documentation, the rash was most likely an allergic reaction to Tegaderm consistent with the patient’s known history.

Patient E: **Moderate rash maculopapular and grade 1 pruritus**

A 57-year-old female with IDC of the left breast and history of allergies to diphenhydramine, oxycodone, and paclitaxel received 67 mg (1 mg/kg) LUMISIGHT. The narrative states that no allergic reaction was reported during the infusion. At an unknown time on the day of IP administration and surgery, AEs of rash maculopapular and pruritus occurred. No action was taken, and the duration of both AEs was 21 days. Tryptase, histamine, and total complement were not assessed.

Based on the limited information provided, this event does not meet criteria for anaphylaxis, as this was a skin-limited reaction. The duration of 21 days is not consistent with anaphylaxis. The nature and etiology of the rash cannot be determined, noting that it was judged related to IP by the investigator.

Patient F: **Moderate urticaria**

A 66-year-old female with stage 2A ILC of the right breast received 62 mg (1 mg/kg) LUMISIGHT. The narrative states that no allergic reaction was reported during the infusion. At an unknown time on the day of IP administration and surgery, AE of urticaria occurred. An unspecified medication was given as treatment, and the AE duration was 11 days. Tryptase, histamine, and total complement were not assessed.

Based on the limited information provided, this event does not meet criteria for anaphylaxis, as this was a skin-limited reaction. The duration of 11 days is not consistent with anaphylaxis.