

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214511Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA 214511 LUMISIGHT (Pegulicianine)**Multi-disciplinary Review and Evaluation****NDA Multi-Disciplinary Review and Evaluation**

Application Type	505(b)(1) NDA
Application Number	214511
Priority or Standard	Priority
Submit Date	March 17, 2023
Received Date	March 17, 2023
PDUFA Goal Date	November 17, 2023
Division/Office	DIRM/OSM
Review Completion Date	April 16, 2024
Established/Proper Name	Pegulicianine
(Proposed) Trade Name	LUMISIGHT
Pharmacologic Class	Optical Imaging Agent
Code name	LUM015
Applicant	Lumicell, Inc.
Dosage form	For injection
Applicant proposed Dosing Regimen	The recommended dose of LUMISIGHT is a single intravenous injection of 1 mg/kg diluted to 10 mg/mL in 0.45% sodium chloride for injection (USP), administered over a 3 minute period. Administer LUMISIGHT 2 to 6 hours prior to imaging.
Applicant Proposed Indication/Population	LUMISIGHT (pegulicianine) for injection is indicated for use in patients with breast cancer to assist in the detection of cancerous tissue within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery. LUMISIGHT is used with Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	254837009 Malignant neoplasm of breast (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	LUMISIGHT is an optical imaging agent indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.
Recommended SNOMED CT Indication Disease Term	372064008 Malignant neoplasm of female breast (disorder)
Recommended Dosing Regimen	The recommended dose of LUMISIGHT is 1 mg/kg actual body weight by intravenous injection over 3 minutes administered 2 hours to 6 hours prior to imaging.

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DEPI= Division of Epidemiology 1

DPACC=Division of Pulmonology, Allergy and Critical Care

Glossary

AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BCS	breast conserving surgery
BLA	biologics license application
BP	blood pressure
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CNS	central nervous system
DARRTS	document archiving, reporting, and regulatory tracking system
DCIS	ductal carcinoma in situ
DVS	Direct Visualization System
ECG	electrocardiogram
FDA	Food and Drug Administration
FN	false negative
FOB	functional observational battery
FP	false positive
GCP	good clinical practice
GLP	good laboratory practice
HS	healthy patients
IDC	invasive ductal carcinoma
IDE	investigational device exemptions
IND	investigational new drug
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NDA	new drug application
NOAEL	no-observed-adverse-effect level
NRU	neutral red uptake
OSI	Office of Scientific Investigation
PEG	polyethylene glycol
PI	prescribing information
PK	pharmacokinetics
SAE	serious adverse event
SLN	sentinel lymph node
SoC	standard of care

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SoT	standard of truth
TK	toxicokinetics
TN	true negative
TP	true positive

1. Executive Summary

1.1. Product Introduction

LUMISIGHT (pegulicianine) is an optical imaging drug constituent of a combination product consisting of LUMISIGHT for injection, and a device constituent, the Lumicell Direct Visualization System (DVS).

LUMISIGHT is a new molecular entity which contains a fluorophore and a quencher connected by a peptide backbone. It is optically inactive as administered and produces a fluorescent signal after its peptide backbone is cleaved by enzymes, including cathepsins and matrix metalloproteases (MMPs), 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. The recommended 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for this NDA is derived from an adequate and well-controlled multicenter clinical trial (CL0007) and confirmatory evidence from a second multicenter clinical trial (CL0006), both conducted by the Applicant. Each study enrolled adult patients with confirmed invasive breast cancer, ductal carcinoma in situ (DCIS), or both, and assessed the proportion of patients receiving LUMISIGHT who had cancer in a LUMISIGHT-guided shave after completion of standard of care (SoC) lumpectomy, as well as tissue-level sensitivity and specificity. In CL0007, 27 of 357 (8%; 95% confidence interval 5%, 11%) patients had cancer confirmed by histopathology in at least one LUMISIGHT-guided shave. The tissue-level sensitivity and specificity were 49% (36%, 62%) and 87% (85%, 88%), respectively. Data from CL0006 were used to develop the tumor detection algorithm for the Lumicell DVS. This study also included a validation cohort that prospectively used the same algorithm as CL0007. In this cohort, 9 of 103 (9%; 4%, 16%) patients had cancer confirmed by histopathology in at least one LUMISIGHT-guided shave. The tissue-level sensitivity and specificity were 64% (41%, 81%) and 80% (76%, 84%), respectively. The review team concluded that LUMISIGHT, when used with the Lumicell DVS, is effective to assist in the detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.

1.3.Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Breast cancer is a life threatening and debilitating disease and is the most common cancer in American women. Breast conserving surgery (BCS) followed by radiotherapy and often endocrine therapy is generally the preferred treatment option for early-stage breast cancer as BCS is less invasive, associated with less morbidity, and has a better cosmetic outcome than mastectomy. Moreover, survival with breast conservation surgery combined with radiation therapy is similar to survival with mastectomy. After BCS, the presence of cancer cells at or near lumpectomy specimen margins is predictive of ipsilateral breast tumor recurrence. 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.

LUMISIGHT is an optical imaging drug constituent of a combination product consisting of LUMISIGHT for injection and a device constituent, the Lumicell DVS. LUMISIGHT is optically inactive as administered and produces a fluorescent signal after its peptide backbone is cleaved by enzymes including cathepsins and MMPs. The fluorescence signal from cleaved pegulicianine is detected by the Lumicell DVS, which displays images and highlights suspected tissue containing cancer within the resection cavity following removal of the primary specimen during lumpectomy surgery.

The efficacy of LUMISIGHT in patients with breast cancer was evaluated in a multicenter clinical trial (CL0007, NCT03686215). A total of 27 of 357 patients had cancer confirmed by histopathology in at least one LUMISIGHT-guided shave (8%; 95% confidence interval 5%, 11%) taken after completion of standard of care (SoC) lumpectomy. The tissue-level sensitivity and specificity were 49% (36%, 62%) and 87% (85%, 88%), respectively. Confirmatory evidence of effectiveness was provided by CL0006 (NCT03321929), which was a multicenter clinical study undertaken to develop the algorithm used by the Lumicell DVS for detection of residual cancer tissue. In the validation cohort of CL0006, 9 of 103 (9%; 4%, 16%) 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 64% (41%, 81%) and 80% (76%, 84%), respectively.

The safety of LUMISIGHT was evaluated in 726 patients with cancer who received a single dose of 1 mg/kg of LUMISIGHT. Among these 726 patients, 703 (97%) had breast cancer. Adverse reactions occurring in $\geq 1\%$ of patients receiving LUMISIGHT were hypersensitivity (4.8%), including 4 cases of anaphylaxis (0.6%), and chromaturia (85%). Another clinically important risk is misdiagnosis caused by false positive (FP) or false negative (FN) findings. The risks of serious hypersensitivity reactions and of misdiagnosis are cited in the Warnings and Precautions section of the prescribing information (PI). Mitigation strategies for serious hypersensitivity reactions are based on active patient monitoring starting

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with the administration of the drug and continuing during the subsequent pre-operative period. A boxed warning is provided to increase awareness of the risk of hypersensitivity, and the Applicant proposes to include education of the risk in the training program for physicians. An observational post-marketing requirement study will be carried out to characterize and better estimate the incidence of anaphylaxis and other serious hypersensitivity reactions. The Applicant will also carry out enhanced pharmacovigilance. These data will allow refinement of the risk mitigation strategies.

Overall, the potential benefit of LUMISIGHT in the indicated patient population outweighs the risks. Therefore, the review team recommends approval of this NDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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	• 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 tumor recurrence and re-excision risks.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	complications, patient distress, surgical pain, and delay of the start of adjuvant radiotherapy; it may also increase the risk of poor cosmetic outcomes.	
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 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	- 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. - Currently available procedures 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.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
Benefit	• 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 (8%) 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% and 87%, respectively. • Overall, 17% of patients had positive margins following standard of care surgery. Among these 62 patients, 15% converted to negative margins following LUMISIGHT-guided surgery (overall conversion rate 3%). 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.	• 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 false positive

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		tissues was high, there is uncertainty regarding the fraction of converters who benefited from the product.
Risk 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 of LUMISIGHT. • Limited information is available on how patients were monitored following the administration of LUMISIGHT in the clinical trial. • False positive and false negative rates of LUMISIGHT should also be considered. Overall, 43% of patients had at least one false positive tissue and 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 with availability of immediate access to emergency treatment. • Multiple risk management and postmarket assessment strategies for hypersensitivity and anaphylaxis will be employed, including a boxed warning, postmarketing study, and enhanced pharmacovigilance.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	8.1.1.2
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	

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☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Breast cancer is a life threatening and 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 reported poorer survival for patients who receive mastectomy compared to those who receive BCS plus radiotherapy ([Agarwal et al. 2014](#); [Fisher et al. 2015](#)). Approximately 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 reoperation for additional tissue resection, because the increased risk of ipsilateral breast tumor recurrence associated with positive margins is not

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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 will undergo 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.

2.2.Analysis of Current Treatment Options

Currently, no FDA-approved intraoperative technology is available to directly examine the lumpectomy cavity for residual cancer after the main specimen is removed in BCS. Instead, perioperative procedures 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, however several devices are marketed for this use, and histopathology methods are also available. [Table 1](#) summarizes currently used intraoperative methods for margin assessment for BCS (Maloney et al. 2018).

Table 1. Methods for Intraoperative Margin Assessment for Breast Conserving Surgery

Categories	Device or Technique
Specimen radiography	Multiple
Dielectric spectroscopy	MarginProbe (P110014)
Histopathology	Frozen sectioning Touch cytology

Source: Adapted from Maloney et al. 2018.

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.

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Histopathology methods for margin detection assess the cellular characteristics of tissue at the microscopic level. Permanent section histopathology currently serves as the gold standard for comparisons with other detection approaches, however as discussed above this method 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 specialized personnel.

While not based on intraoperative margin assessment, the operative practice of comprehensive shaving should also be mentioned. This procedure 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.

3. Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

LUMISIGHT is a new molecular entity and is not currently marketed in the United States.

3.2.Summary of Presubmission/Submission Regulatory Activity

The following is a summary of the regulatory history of LUMISIGHT relevant to this review:

- 04/19/2011: Clinical development of the LUMISIGHT and Lumicell DVS combination product started under IND 111670 to evaluate the initial safety of LUMISIGHT in a Phase 1, first-in-human study.
- 09/13/2013: 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 (RFD130077). After this designation, clinical development for the breast cancer indication was conducted under IDE G140195.
- 03/28/2018: A Breakthrough Device designation was granted for the LUM Imaging System for use in patients undergoing breast conserving surgery for breast cancer.
- 10/29/2020: Fast Track designation was 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.
- 11/16/2020: Pre-NDA meeting
- 07/15/2021: Part 1 rolling NDA submission
- 11/11/2021: Part 2 rolling NDA submission

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- 03/08/2023: Part 3 rolling NDA submission
- 03/17/2023: Part 4 rolling NDA submission (final component of the NDA including clinical data).
- 04/14/2023: Premarket application P230014 submission to CDRH for Lumicell DVS.

Key discussion points during development related to the design, endpoints, and data analysis for CL0007 are summarized below:

- Implementation of a control arm: FDA recommended that a control arm should be added to introduce uncertainty to the surgeon on whether the Lumicell DVS would be used after SoC. The aim would be to minimize potential bias in the resection of equivocal tissue during the SoC procedure. The Applicant agreed with this recommendation and incorporated a control arm with a 10:1 device arm to control arm randomization ratio.
- Sensitivity and specificity as primary endpoints: FDA recommended that to evaluate the diagnostic performance of the system, tissue-level sensitivity and specificity should be included as primary endpoints. In a subsequent discussion, FDA agreed with the Applicant to use a hierarchical approach for establishing the truth standard to be used in the calculation of sensitivity and specificity.
- Definition of positive margins for pure DCIS: FDA recommended a definition of positive margins for pure DCIS as tumor found less than 2 mm from the inked surface of specimens, based on lower rates of ipsilateral breast tumor recurrence associated with such margins ([Morrow et al. 2016](#)).
- Blinding the source of shave from the pathologist: Per recommendation from FDA, the Applicant implemented a process to blind the pathologist on whether the tissue shave being processed and analyzed by pathology was a SoC shave or a LUMISIGHT-guided shave to minimize potential interpretation bias.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

As CDRH is the lead center for the review of this combination product, Office of Scientific Investigation (OSI) audits of clinical sites were coordinated by CDRH. Four clinical sites involved in study CL0007 were inspected and OSI reported no important concerns. An inspection of the Applicant's facility resulted in issuance of a form FDA-483 for failure to ensure proper monitoring. CDRH classified the inspection as voluntary action indicated and the Applicant's corrective actions were considered adequate.

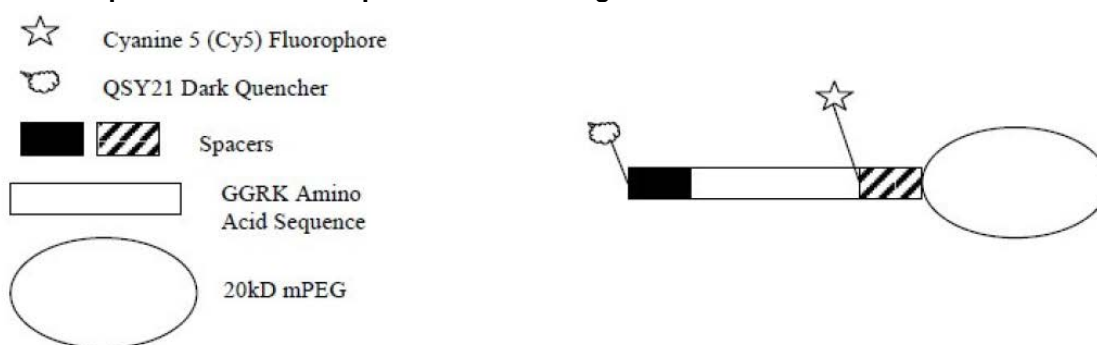
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4.2.Product Quality

Pegulicianine for injection is a (b) (4) single-dose, lyophilized powder that contains the active ingredient pegulicianine as an acetate salt, mannitol (b) (4) and sodium phosphate (b) (4). Pegulicianine is a fluorescent dye containing a fluorophore (Cy5 monoacid), a dark quencher (QSY21 carboxylic acid), an amino acid backbone, and a polyethylene glycol (PEG) moiety (methoxy-PEG, ~20k Dalton), as shown schematically in [Figure 1](#). Pegulicianine produces a fluorescent signal after its peptide backbone is cleaved by the proteases in tumor tissue.

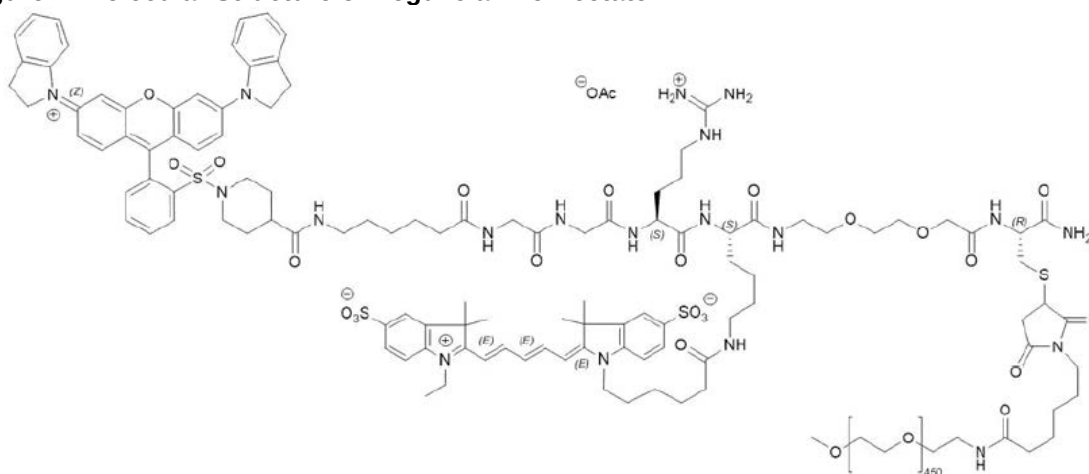
Figure 1. Simplified Structural Representation of Pegulicianine



Source: Figure 1 of module 2.6.1 Pharmacology Introduction
Abbreviations: kD = kilodaltons, mPEG = methoxypolyethylene glycol

The structural formula of pegulicianine acetate is shown in [Figure 2](#).

Figure 2. Molecular Structure of Pegulicianine Acetate



Source: Figure 2 of module 2.3 Quality Overall Summary

Each vial contains 40 mg of pegulicianine in a dark blue lyophilized powder for reconstitution in 4 mL of 0.45% sodium chloride for injection. The extractable volume of the reconstituted drug

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product is determined by gravimetric analysis, and it is 3.9 mL. The strength of the drug product is 39 mg, and the concentration is 10 mg/mL. The Applicant listed six impurities as specified impurities by RRT ranges based on our recommendation and acceptance criteria that were established based on non-clinical data. The acceptance criterion for unspecified impurities was (b) (4) based on FDA's recommendation. The recommended dose of LUMISIGHT is 1 mg/kg. (b) (4) The drug product is manufactured by (b) (4) and the drug substance by (b) (4). The drug substance and drug product facilities are GMP compliant and recommended for approval to support this NDA. The drug product is supplied in a (b) (4) 10-mL glass vial with grey (b) (4) rubber stopper with crimp and blue flip-off seal. The shelf life of the drug product is 36 months when stored at $-20 \pm 5^{\circ}\text{C}$.

Reference is made to the Office of Product Quality Integrated Quality Assessment dated November 08, 2023, which is filed in DARRTS. The product quality reviewers recommend approval of the application.

4.3.Clinical Microbiology

This section is not applicable to this NDA.

4.4.Devices and Companion Diagnostic Issues

LUMISIGHT is the drug constituent of a device-drug combination product. A separate marketing application has been submitted to CDRH for the Lumicell DVS device component, and reference is made to the P230014 review for evaluation of device-related issues. The CDRH reviewers recommend approval of the device submission.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA can be approved from a nonclinical perspective.

The Applicant conducted nonclinical studies that support the marketing authorization of the optical imaging agent, LUMISIGHT (pegulicianine, LUM015), at the proposed clinical dose of 1 mg/kg for fluorescence imaging in adults with breast cancer.

The recommendation to approve the NDA is based on nonclinical findings that established specificity, proof-of-concept, adequate margins of safety (15-fold safety margin for extended single-dose toxicity studies in rats and 4.8-fold safety margin for repeat-dose toxicity studies in rabbits; margins were 52.7-fold and 11.6-fold by area under the curve [AUC] in rats and rabbits, respectively), and absence of important toxicological findings. The pivotal studies include proof-

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of-concept studies in mice and dogs, single and repeat dose general toxicity studies with safety pharmacology and toxicokinetic (TK) endpoints (rats, rabbits, and dogs), and in vitro and in vivo genotoxicity studies.

In Vitro and In Vivo Pharmacology Studies

Proof-of-concept studies were conducted in mice and dogs primarily to demonstrate proteolytic activation of the probe and tumor visualization in xenograft tumor models (mice) and naturally occurring tumors (dogs).

Safety Pharmacology

There were no significant safety findings identified for pegulicianine for any of the safety pharmacology parameters reported in neurobehavioral (functional observational battery [FOB]) assessments conducted as part of an expanded acute intravenous (IV) toxicity study in Sprague Dawley rats (up to 93 mg/kg), cardiovascular, electrocardiogram (ECG) and respiratory assessments conducted in a 7-day IV toxicity study in Beagle dogs (up to 0.5 mg/kg), and heart rate and body temperature evaluations conducted in a 7-day IV toxicity study in New Zealand White rabbits (up to 15 mg/kg). Signs of hypoactivity, ataxia, and prostration were observed in the single-dose rat study in males treated with a pegulicianine-derived fragment containing the QSY21 non-fluorescent quencher (referred to as Fragment 1) at dose level of 11.24 mg/kg.

Pharmacokinetics/Absorption, Distribution, Metabolism, Excretion

The plasma pharmacokinetics (PKs) of pegulicianine was determined in good laboratory practice (GLP) toxicology studies conducted in rats, dogs, and rabbits. There were no important sex differences in systemic exposure by AUC₀₋₂₄ for pegulicianine and Fragment 1 in Sprague Dawley rats. There were no apparent sex differences in systemic exposure for pegulicianine in New Zealand white rabbits and no important accumulation of pegulicianine following daily IV administration for 7 days.

Single- and Repeat-Dose Toxicology

Extended single-dose and repeat-dose toxicity and TK studies of pegulicianine were conducted in Sprague Dawley rats, New Zealand White rabbits, and Beagle dogs. There was blue discoloration of tissues (injection site and lung) and urine that was related to the color of pegulicianine and Fragment 1 and not considered adverse. Based on the findings of the rat study, the administered high dose of 93 mg/kg was determined to be the no-observed-adverse-effect level (NOAEL) with a 15-fold safety margin (by body surface area scaling) based on the proposed clinical dose of 1 mg/kg. There was also blue discoloration observed in repeat-dose studies in New Zealand White rabbits and Beagle dogs that was related to the dark blue color of the test article. Beagle dogs demonstrated dose-limiting clinical observations of hypersensitization (swelling, hypoactivity, salivation) at 1 and 10 mg/kg/day. Based on the

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findings of repeat-dose toxicity studies, the NOAELs were 0.5 mg/kg/day and 15 mg/kg/day, respectively in dogs and rabbits. The safety margin based on the repeat-dose rabbit study was 4.8-fold (by body surface area scaling) based on the proposed clinical dose of 1 mg/kg.

An adequate safety margin was not demonstrated in the repeat-dose toxicity study in dogs primarily due to important dose-related hypersensitivity reactions which included facial swelling, swelling of the ears and limbs, hypoactivity, and salivation. At the proposed clinical dose of 1 mg/kg, the dose margin was 0.28-fold by body surface area scaling. Signs of hypoactivity, ataxia, and prostration were observed in male rats following intravenous administration of Fragment 1 at 11.24 mg/kg only, and not pegulicianine, which the Applicant attributed to the infusion rate. The dose-related adverse findings observed in both species (absent in the rabbit) are informative of the hypersensitivity reactions observed in humans.

Genotoxicity, Carcinogenicity, and Reproductive Toxicity

Developmental and reproductive toxicity studies were not required for pegulicianine. The Applicant requested to omit these studies and the Agency concluded that this was acceptable based on the proposed single-use indication, target population, and absence of reproductive organ toxicity findings from single- and repeat-dose toxicity studies in rats, rabbits, and dogs. Carcinogenicity studies were not conducted and are not required for this single-use optical imaging agent.

Other Nonclinical Studies

No other nonclinical studies are necessary to support the safety of pegulicianine for the proposed indication in the intended population.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

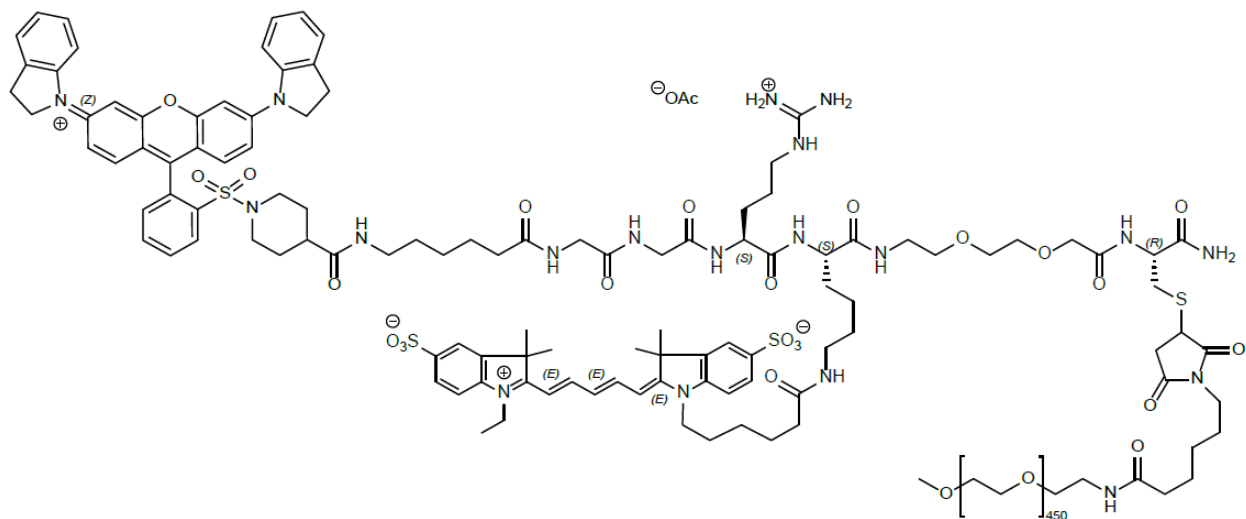
5.3.1. Introduction

Pegulicianine is composed of a near infrared fluorescent cyanine dye (Cy5), a non-fluorescent amine quenching chromophore or dark quencher (QSY21), an amino acid backbone, two spacers (6-aminohexanoic acid or ϵ Ahx and PEG2), and a 20kDa PEG molecule. When the amino acid backbone is cleaved by cathepsin enzymes that are upregulated in cancerous tissue, the Cy5-containing fluorescent molecule is no longer quenched by QSY21 and can be detected by the Lumicell DVS. The pharmacology of pegulicianine as described in this review is comprised of in vivo proof-of-concept studies in mouse xenograft models and dogs with tumors. The structure of pegulicianine is shown in [Figure 1](#) (Section [4.2](#)) and [Figure 3](#).

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Figure 3. Chemical Structure of Pegulicianine



Source: Applicant's Figure, eCTD section 2.6.1.1.

Note: CAS Registry No.: 2230217-17-9

Note: Molecular Structure = (QSY21)-εAhx-Gly-Gly-Arg-Lys(Cy5)-AEEAc-Cys(mPEG20,000)-NH₂

Note: Molecular Weight = approximately 22,078 Da (specification is 20.0 kDa to 25 kDa due to PEG molecular mass variability)

Abbreviations: Ahx = Aminohexanoic acid, Arg = arginine, CAS = Chemical Abstracts Service, Cys = cysteine, Da = Daltons, eCTD = electronic technical document, Gly = glycol, kDa = kilodaltons, Lys = lysine, NH₂ = amine, PEG = polyethylene glycol

5.3.2. Mechanism of Action and Proof-of-Concept Studies

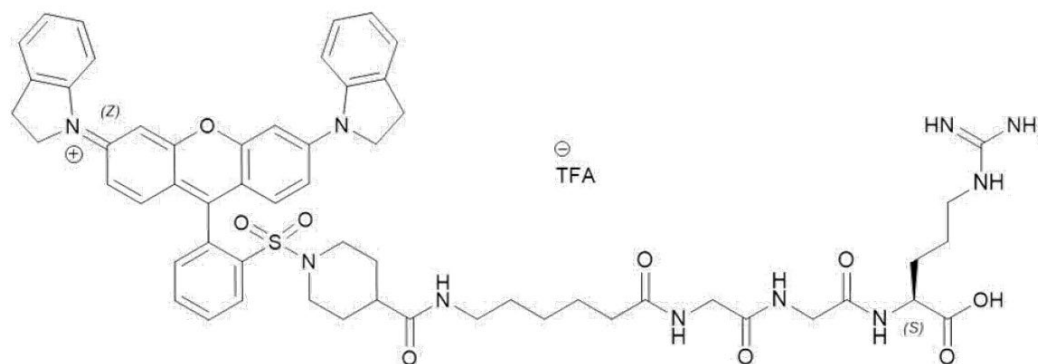
Mechanism of Action:

The mechanism of action of pegulicianine as an optical imaging agent involves producing a near-infrared fluorescent signal (emission between 670 – 700 nm based on imaging system) after the peptide backbone is cleaved by proteases that are overexpressed by tumors, such as cathepsins ([Whitley et al. 2016](#)). After proteolytic cleavage, pegylated near infrared fluorescent dye Cy5 (fragment 2 shown below) is no longer quenched by QSY21 (Fragment 1). In addition, a smaller fluorescent fragment (Fragment 3 shown below) is generated and consists of the Cy5 dye and lysine. The Cy5 dye present in both Fragment 2 and Fragment 3 generates a fluorescence signal when excited with photons at the appropriate wavelength. The chemical structures of the QSY21-containing and Cy5-containing proteolytic fragments are shown below ([Figure 4](#), [Figure 5](#), [Figure 6](#)).

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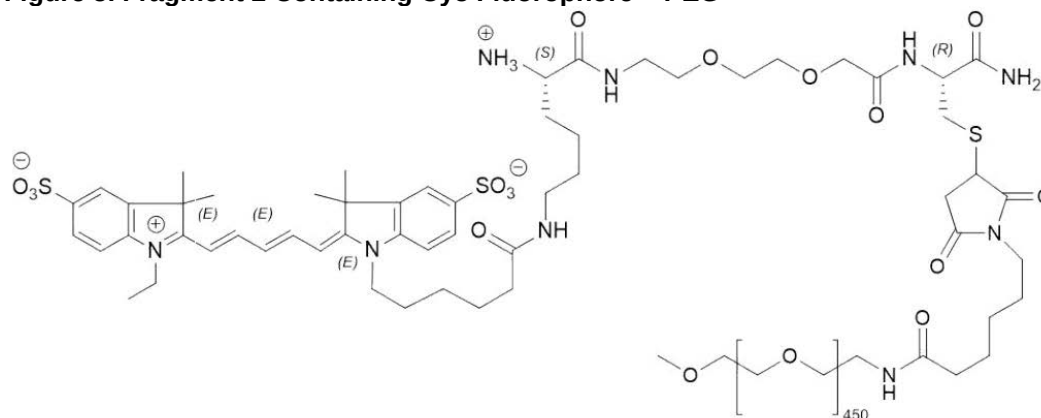
Figure 4. Fragment 1 Containing QSY21 (Non-Fluorescent Quencher)



Source: Applicant's Figure, eCTD section 2.6.1.1

Abbreviations: Ahx = Aminohexanoic acid, Arg = arginine, Cys = cysteine, eCTD = electronic technical document, Gly = glycol, OH = hydroxide, TFA = sodium trifluoroacetate

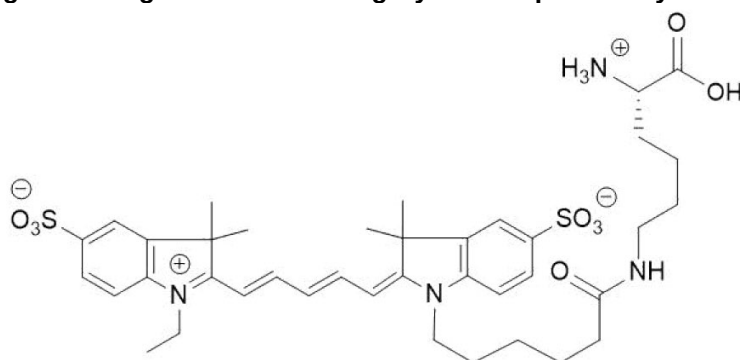
Figure 5. Fragment 2 Containing Cy5 Fluorophore + PEG



Source: Applicant's Figure, eCTD section 2.6.1.1

Abbreviations: eCTD = electronic technical document, PEG= polyethylene glycol

Figure 6. Fragment 3 Containing Cy5 Fluorophore + Lysine



Source: Applicant's Figure, eCTD section 2.6.1.1

Abbreviations: eCTD = electronic technical document

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Proof-of-Concept Studies:

No primary or secondary pharmacodynamic studies were conducted with pegulicianine. The Applicant provided the nonclinical pharmacology data below from published studies conducted with pegulicianine to support the NDA submission.

The use of fluorescent signal liberated by protease cleavage of probes in tumor tissue as a potential aid in surgical intervention has been established using mouse ([Mito et al. 2012](#); [Cuneo et al. 2013](#)) and canine models ([Eward et al. 2013](#)). Pegulicianine administration in a mouse model of soft-tissue sarcoma resulted in signal contrast between tumor and normal tissue (tumor-to-normal tissue ratio). The authors of the study interpreted the findings of residual fluorescence within the tumor bed to be highly predictive of local recurrence, thus suggesting that this intraoperative imaging technique could be an adjunct to surgery and tailor adjuvant therapy ([Whitley et al. 2016](#)). Naturally occurring cancers were evaluated in a study of 21 dogs to demonstrate the performance of the pegulicianine in a larger animal model (Applicant collaboration with Tufts University School of Veterinary Medicine and Veterinary Specialty Hospital of the Carolinas). Dogs were administered pegulicianine at dose levels that ranged from 0.5 mg/kg to 2.0 mg/kg. Following the initial tumor resection, no residual fluorescence was found in the tumor beds of 20 dogs, findings which were confirmed by pathology. Moreover, pegulicianine detected residual cancer in the tumor bed in one dog and the surgeon continued the surgery until no residual fluorescence was detected. Pathology confirmed that after the initial resection, the dog had positive tumor margins but after removal of all the fluorescent tissue, negative margins were obtained. The nonclinical proof-of-concept findings supported the potential utility of pegulicianine to assist the surgeon in detection of abnormal tissue. The dog study demonstrated 93% sensitivity and 95% specificity of pegulicianine compared with histopathology at tissue-level ([Table 2](#)).

Table 2. Tissue-level Sensitivity and Specificity of Pegulicianine in Dogs Undergoing Resection of Naturally Occurring Tumors

Fluorescence	Histopathology Reference	
	Abnormal	Normal
Positive	28	3
Negative	2	63

Source: Adapted from Applicant's Table, eCTD section 2.6.2

Abbreviations: eCTD = electronic technical document

There were reports of hypersensitivity reaction in form of mild facial flushing and itchiness shortly after pegulicianine administration in 10 dogs. The reaction subsided within an hour following administration of diphenhydramine. No additional adverse events (AEs) were reported. According to the Applicant, there were no clinical chemistry findings from the first eight dogs when comparing values obtained prior to pegulicianine injection (baseline) and 24 hours and 48 hours post-injection.

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5.3.3. Safety Pharmacology

Summary of Safety Pharmacology Studies:

Stand-alone safety pharmacology studies of pegulicianine were not conducted. The Applicant incorporated the safety pharmacology endpoints (central nervous system [CNS], respiratory, and cardiovascular safety) into the conducted rodent (CNS FOB in expanded single-dose toxicity study in rats, Study No. 51103-11-620) and nonrodent toxicity studies (cardiovascular and respiratory endpoints in repeat-dose toxicity study in dogs, Study No. 2330-010-001, and heart rate and body temperature in rabbits, Study No. 51103-15-205) to support the NDA. The results of the safety pharmacology endpoints demonstrated no undesirable pharmacodynamic effects of pegulicianine on physiological functions at the dose levels tested.

5.3.4. Evaluation of the CNS

Study Title/Number: An Acute Toxicity Study of LUM015 and Fragment 1 Following Single Intravenous Administration in Sprague-Dawley Rats / 51103-11-620

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of the FOB was to examine the potential effect of pegulicianine and Fragment 1 on a battery of behavioral and physiological parameters covering central and peripheral nervous system functions following IV administration of 9.3 and 93 mg/kg pegulicianine, 11.24 mg/kg Fragment 1, or negative control (water for injection) in male Sprague Dawley rats (n=5/group, 7 – 8 weeks of age). CNS FOB parameters (home cage, hand-held, open-field, elicited responses, physiological measurement) were evaluated prior to dosing (0 hour), post-dosing, and prior to terminal sacrifice (Study Day 3).

Key Findings

- A single IV injection (slow bolus administered over 1 minute) of pegulicianine at 9.3 or 93 mg/kg to male Sprague Dawley rats did not significantly affect FOB parameters.
- Administration of 11.24 mg/kg Fragment 1 resulted in death of one male following dosing. Observations included signs of hypoactivity, ataxia, and prostration in males only. Findings were attributed to more rapid IV injection in males compared to females in the study.
- There were no clinical signs or mortalities up to terminal sacrifice following a single IV injection of pegulicianine at any of the dose levels evaluated.

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Conclusion

A single IV injection of pegulicianine at 9.3 and 93 mg/kg (15-fold the clinical dose of 1 mg/kg) to Sprague Dawley rats did not affect behavioral or physiological parameters representative of main central and peripheral nervous system functions. Administration of Fragment 1 containing QSY21 resulted in one mortality and CNS signs of hypoactivity, ataxia, and prostration at 11.24 mg/kg (25-fold the clinical dose of 1 mg/kg).

5.3.5. Cardiovascular and Respiratory Assessment in Dogs

Study Title/Number: Repeat-Dose Toxicity Study of NSC-D774650-T in Beagle Dogs / 2330-010-001

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of the study was to examine the effects of pegulicianine at up to 10 mg/kg on cardiovascular ECG parameters (blood pressure was not measured) and respiratory function (rate, tidal volume, minute volume) following IV administration in conscious Beagle dogs (n=2/group, 6 – 7 months of age). ECGs were obtained pre-test, six times during the dosing period (1, 6, and 24 hours post-infusion on Day 1 and Day 9), and once during the recovery period (Day 23). Respiratory assessment by pneumotachograph was performed once pre-test and on Days 2, 9, and 23.

Key Findings

- No treatment-related effects on body temperature were observed.
- No abnormal ECG or respiratory treatment-related effects were observed.
- No treatment-related effects on heart rates were observed.
- Facial swelling, swelling of the ears and limbs, hypoactivity, and salivation were observed at the 1.0 and 10 mg/kg dose levels. Based on the findings in the dog study, the NOAEL for pegulicianine was determined to be 0.5 mg/kg.

Conclusion

Cardiovascular and respiratory pharmacology endpoints were evaluated as part of a 7-day IV toxicity study in dogs (Study No. 2330-010-001). Significant hypersensitivity reactions occurred, and the treated group 2 dose level was reduced from 1 mg/kg to 0.5 mg/kg on Day 3. No abnormal heart rate, ECG, or respiratory treatment-related effects were reported during the study and a NOAEL of 0.5 mg/kg was obtained.

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5.4.ADME/PK

No absorption, distribution, or excretion studies were conducted with pegulicianine. Plasma PKs of pegulicianine were determined in the TKs studies conducted as part of GLP toxicology studies in rat, dog, and rabbit ([Table 3](#)).

Table 3. Summary of ADME/PK Data

Type of Study	Major Findings
<i>Absorption</i>	
Please see PK data for rats, dogs, and rabbits reported following excretion.	
<i>Distribution</i>	
No distribution studies were conducted with pegulicianine.	
<i>Metabolism</i>	
A Mouse-human Phase 1 Co-clinical Trial of a Protease-activated Fluorescent Probe for Imaging Cancer (Whitley et al. 2016)	An in vitro protease assay (cathepsins and trypsin) was conducted to demonstrate proteolytic cleavage of pegulicianine and increased fluorescence of Cy5 fragments. HPLC analysis of plasma from mice and humans administered pegulicianine demonstrated proteolytic activation and formation of fluorescent Cy5-containing fragments.
In Vitro Stability of Pegulicianine in Cryopreserved Human Hepatocytes (MC22M-0055)	Under the conditions of this in vitro study, pegulicianine (Lot #: B18090081, Purity %: 98.6%) was metabolically stable ($\geq 95\%$ parent compound remaining) up to 240 min incubation with human hepatocytes (20 donors, mixed gender) and no additional components or metabolites were observed. Pegulicianine fragments 1 – 3 were not evaluated in the assay.
In Vitro Metabolism of Pegulicianine by Recombinant Human Cytochrome P450 Enzymes (MC22M-0054)	Under the conditions of this in vitro study, pegulicianine (Lot #: B18090081, Purity %: 98.6%) was moderately stable following incubation with recombinant human cytochrome P450 enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 with 83.4%, 80.3%, 81.6%, 78.9%, 73.4%, 82.5% and 84.4% remaining after 60 min incubation, respectively. Pegulicianine fragments 1 – 3 were not evaluated in the assay.
Determination of the Potential Inhibition (IC ₅₀) of Human CYP Isozymes by LUM015 (MC22M-0056)	Under the conditions of this in vitro study, pegulicianine (Lot #: B18090081, Purity %: 98.6%) weakly inhibited recombinant human cytochrome P450 enzymes 1A2, 2B6, 2C8, and 2C19 with IC ₅₀ values estimated to be greater than 25 $\mu\text{g/mL}$. No inhibition was observed for isoforms 2C9, 2D6, and 3A4 at 25 $\mu\text{g/mL}$, the highest concentration evaluated in the assay. Pegulicianine was not considered to be an inhibitor of human cytochrome P450 enzymes. Pegulicianine fragments 1 – 3 were not evaluated in the assay.
<i>Excretion</i>	
No excretion studies were conducted with pegulicianine.	

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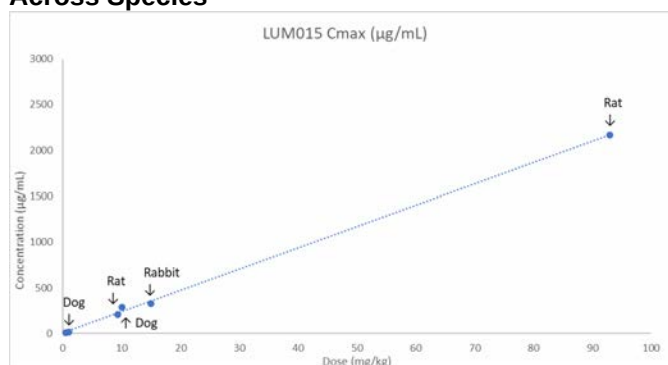
Type of Study	Major Findings
<i>TK data from general toxicology studies</i>	
An Acute Toxicity Study of LUM015 and Fragment 1 Following Single Intravenous Administration in Sprague-Dawley Rats (51103-11-620)	Systemic exposure: Systemic exposure increased as dose increased from 9.3 to 93 mg/kg in a dose-proportional manner. There were no significant sex differences in exposure expressed as AUC ₀₋₂₄ . For half-life (5.36 – 6.84 hr), systemic clearance (9.22 – 11.7 mL/hr/kg), and apparent volume of distribution (75.6 – 106 mL/kg) during the terminal phase, data were inadequate to determine trends regarding sex or dose level.
A 7-Day Toxicity and Toxicokinetic Study of LUM015 Following Intravenous Administration in New Zealand White Rabbits with a 14-Day Recovery Phase (51103-15-205)	Plasma concentration: Plasma concentrations of pegulicianine (determined indirectly through assay of Fragment 1) were measurable in all animals from 5 min-24 h post-dose at 15 mg/kg dose level on Days 1 and 7. Plasma concentrations decreased rapidly through 1 hr post-dose and then gradually from 1 hr post-dose through 24 hr on both TK days. Systemic exposure: Dose-proportionality was not determined because only a single dose level was evaluated in the study. There were no significant sex differences in exposure expressed as AUC _{0-t} (1,400 – 1,930 hr·µg/mL) or half-life (5.01 – 6.91 hr). No significant accumulation was observed following daily dosing for 7 days by C _{max} (1.11 and 1.03 for males and females, respectively) and AUC _{0-t} (1.27 and 1.23 for males and females, respectively)
Repeat-Dose Toxicity Study of NSC-D774650-T (LUM015) in Beagle Dogs (2330-010-001)	Plasma concentration: Plasma concentrations of pegulicianine (determined indirectly through assay of Fragment 1) were measurable in all animals from 5 min through 24 hr post-dose at 1/0.5 and 10 mg/kg dose levels for pegulicianine on Days 1 and 8. Plasma concentrations decreased rapidly through 1 hr post-dose and then gradually from 1 hr post-dose through 24 hr on both TK days. Systemic Exposure: Systemic exposure (by C _{max} , AUC _{last} , and AUC _{INF}) increased as dose increased 10-fold from 1 to 10 mg/kg (Day 1) and 20-fold from 0.5 to 10 mg/kg (Day 9) in an approximately dose-proportional manner. There were no significant sex differences in exposure, half-life (7 – 8 hr), and clearance (10 mL/hr/kg on Day 1 and 8 mL/hr/kg on Day 8). No significant accumulation was observed following dosing for 8 days by C _{max} ; accumulation by AUC ranged from 1.24 to 1.30 for the low dose group (1/0.5 mg/kg) and from 1.36 to 1.78 for the high dose group (10 mg/kg). Study deviation resulted in dose level being reduced from 1 to 0.5 mg/kg for the low dose group.

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Type of Study	Major Findings
Plasma AUC and $C_{\max}$ vs. Dose Across Species (Study Summary)	TK data across rats, dogs, and rabbits demonstrated reasonable dose proportionality of plasma pegulicianine concentrations. Plasma half-life ranged from 5 – 8 hr. There was no accumulation based on $C_{\max}$ values; however, AUCs over the exposure period showed a slight or minimal accumulation in rabbits and dogs. Pegulicianine demonstrated a relatively small volume of distribution and low plasma clearance rate that was similar between rats and dogs. There were no sex differences in the TK properties for pegulicianine. Figures below show linearity with plasma exposure and dose in mg/kg between species. The Applicant suggested that body weight may more accurately predict exposure across species rather than body surface area adjustment.

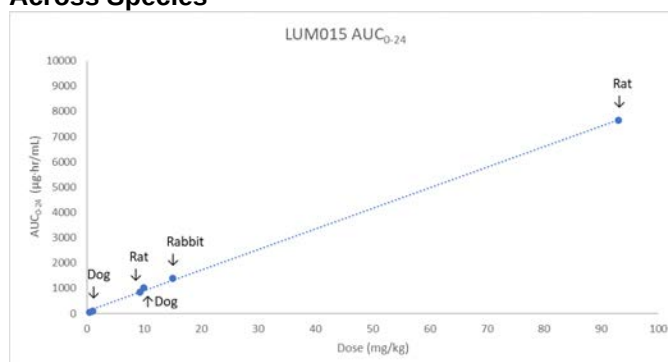
Figure 7. Pegulicianine Plasma $C_{\max}$ vs. Dose Level Across Species



Source: Applicant's Figure, eCTD section 2.6.4

Abbreviations: $C_{\max}$ = maximum plasma concentration, eCTD = electronic common technical document, LUM015 = LUMISIGHT

Figure 8. Pegulicianine Plasma AUC vs. Dose Level Across Species



Source: Applicant's Figure, eCTD section 2.6.4

Abbreviations: AUC₀₋₂₄ = area under the curve from 0 to 24 hrs, eCTD = electronic common technical document, LUM015 = LUMISIGHT

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Type of Study	Major Findings
<i>TK data from carcinogenicity studies</i>	
No carcinogenicity study was conducted, and none was needed.	

Source: Reviewer's Table

Abbreviations: ADME = absorption, distribution, metabolism, excretion, AUC = area under the curve, AUC_{0-t} = the area under the curve up to the last quantifiable time-point, AUC_{INF} = area under the curve from 0 to infinity, AUC_{last} = area under the curve from dosing to the time of the last measured concentration, C_{max} = maximum plasma concentration, HPLC = high-performance liquid chromatography, PK = pharmacokinetics, TK = toxicokinetics

5.5.Toxicology

5.5.1. General Toxicology

Toxicological evaluation of pegulicianine and/or Fragment 1 (containing QSY21 non-fluorescent quencher) was conducted in mice, rats, rabbits, and dogs. The clinically relevant route of exposure (IV injection) was used for all in vivo toxicology studies which included acute single-dose (rats and rabbits) and repeat-dose toxicology (rabbits and dogs), and genotoxicity studies (in vivo micronucleus assessment of Fragment 1 in mice). An expanded single-dose IV (slow bolus) toxicity study with 14-day recovery and TK assessment was conducted with pegulicianine and Fragment 1 at up to 93 mg/kg and 11.24 mg/kg, respectively, in rats (Study No. 51103-11-620); a non-GLP single-dose IV toxicity study with 10 mg/kg pegulicianine was also conducted in rabbits (Study No. 51103-14-167). Additional 7-day and 8-day repeat-dose toxicity studies with TK assessment were conducted with pegulicianine at 15 mg/kg in rabbits (Study No. 51103-15-205) and up to 10 mg/kg in dogs (Study No. 2330-010-001), respectively.

5.5.1.1. Single Dose Toxicity

Single Dose Toxicity Study in Rats

Study title/ number: An Acute Toxicity Study of LUM015 and Fragment 1 Following Single Intravenous Administration in Sprague-Dawley Rats / 51103-11-620

- Pegulicianine was not associated with any dose-related clinical findings, and all rats survived to scheduled necropsies. Based on the absence of any toxicologically relevant findings, the NOAEL was 93 mg/kg (the highest dose tested). Systemic exposure (C_{max} and AUC_{0-24}) at the NOAEL was 2,170 $\mu\text{g/mL}$ and 7,640 $\mu\text{g}\cdot\text{h/mL}$, respectively, for males and 2,580 $\mu\text{g/mL}$ and 9,210 $\mu\text{g}\cdot\text{h/mL}$, respectively, for females. On an AUC basis, the dose margin was 34.6-fold (males) and 41.7-fold (females) the proposed clinical dose of 1 mg/kg per administration.
- No pegulicianine-treated animals died following a single IV injection, and there were no test article-related clinical observations, effects on body weight or body weight change, or effects on food consumption throughout the study.
- Macroscopic findings at the primary necropsy were limited to green discoloration in the kidneys and injection site at the high dose; findings correlated with green discoloration of the urine at the high dose. There were no histologic correlates for the green discoloration in these tissues for pegulicianine.

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- Fragment 1 was associated with urinalysis findings (amorphous sediment, green flake or strip) as well as macroscopic and corresponding histopathologic findings in the lungs that included intracellular blue-green material in macrophages or multinucleated cells, minimal to mild granulomatous inflammation, and minimal hemorrhage. Findings for Fragment 1 were partly reversible by study day 15 (recovery).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 4. Methods for Study No.: 51103-11-620

Methods	Details
Dose and frequency of dosing	0 (vehicle), 9.3 (LD), 93 (HD) mg/kg pegulicianine; 11.24 mg/kg Fragment 1; single dose administration
Route of administration	Intravenous
Formulation/vehicle	Pegulicianine (Lot #: RD111129, %purity: 99.2%), Fragment 1 (Lot #: 2502070, %purity: 96.2)/ WFI
Species/strain	Rats/Sprague-Dawley [CrI:CD(SD)]
Number/sex/group	5/sex/group for main study and 5/sex/group for recovery; 3/sex/group for fragment 1 for main study and recovery (F only)
Age	7 – 8 weeks of age at dosing
Satellite groups/ unique design	TK satellite, n=6/sex/group for pegulicianine and n=3 for vehicle control
Deviation from study protocol affecting interpretation of results	No

Source: Reviewer's Table

Abbreviations: HD = high dose, LD = low dose, TK = toxicokinetics, WFI = water for injection

Table 5. Observations and Results: Changes from Control (Study No. 51103-11-620)

Parameters	Major Findings
Mortality	There were no deaths of pegulicianine-treated animals. One male was found dead following administration of Fragment 1. All other animals survived to scheduled necropsies.
Clinical signs	No significant test-article related findings
Body weights	No test-article related effects on body weights
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
Hematology	No test article-related effects on hematology parameters
Clinical chemistry	No treatment-related effects on serum chemistry
Urinalysis	Green discoloration of the urine at the HD. Amorphous sediment (green in color) observed at the HD and Fragment 1 on necropsy day 3 and 15 and was partly reversible. Findings were considered related to the green discoloration of the kidneys.
Gross pathology	Green discoloration of the kidney and injection site at the HD; green discoloration of the lung in 3M and 3F administered Fragment 1 was partly reversible by study day 15 (recovery).
Organ weights	No test article-related effect on organ weights

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Parameters	Major Findings
Histopathology Adequate battery: Yes	No pegulicianine-related histopathologic findings at terminal necropsy. For Fragment 1, blue-green material observed in macrophages or multinucleated cells of the lungs with minimal to mild granulomatous inflammation and minimal hemorrhage. No histopathologic findings associated with diffuse dark or dark grey discoloration of the renal cortex in HD males (5 of 5) and females (2 of 5). Findings for Fragment 1 were partly reversible by study day 15 (recovery).

Source: Reviewer's Table

Abbreviations: F = female, HD = high dose, M = male

5.5.1.2. Repeat Dose Toxicity

Repeat Dose Toxicity in Beagle Dogs

Study title/ number: Repeat-Dose Toxicity Study of NSC-D774650-T in Beagle Dogs / 2330-010-001

- Beagle dogs were administered pegulicianine at 0.5 or 1.0 mg/kg and 10 mg/kg/day daily for 8 days. Low dose was reduced from 1.0 to 0.5 mg/kg after dosing day 1 during the study.
- Adverse clinical signs not limited to hypersensitivity were observed at both 1 and 10 mg/kg doses but subsided with continued dosing at the 0.5 mg/kg dose level, and the NOAEL was considered the lower dose of 0.5 mg/kg/day.
- The study was not considered adequate to support safety due to study deviation (dose reduction following hypersensitivity reactions) and insufficient animal numbers per treatment group. The repeat-dose toxicity study in rabbits was considered the definitive nonclinical study in a nonrodent species to determine safety margins.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

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Table 6. Methods for Study No.: 2330-010-001

Methods	Details
Dose and frequency of dosing	0 (vehicle), 1.0 (LD), 10 (HD) mg/kg/day pegulicianine; daily for 7 days
Route of administration	Intravenous
Formulation/vehicle	Pegulicianine (Lot #: 11511113, %Purity: 96.8%)/0.45% sodium chloride (saline)
Species/strain	Dog/Beagle
Number/sex/group	2/sex/group for main study and 2/sex/group for recovery
Age	6 – 7 months at dosing
Satellite groups/ unique design	No
Deviation from study protocol affecting interpretation of results	Yes The LD was reduced from 1 mg/kg/day to 0.5 mg/kg/day following hypersensitivity reactions on Day 1 with a 2-day treatment-free period before dosing on Day 3 through Day 9.

Source: Reviewer's Table

Abbreviations: HD = high dose, LD = low dose

Table 7. Observations and Results: Changes from Control (Study No.: 2330-010-001)

Parameters	Major Findings
Mortality	No mortality reported. All employed survived until scheduled necropsy on Day 1 or 24
Clinical signs	Treated dogs exhibited swellings and redness in several parts of the body including swelling of the face (e.g., muzzle, eyes), ears, forelimb and hindlimb with redness on the ears, red sclera, red and raised spots, ventral body surface. There were also discolored (blue/green) urine, salivation, hypoactivity, loose stool, vomiting and labored breathing in the animals. However, these observations subsided post dosing, and disappeared three hours after treatment.
Body weights	No significant weight change reported
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
ECG	No test article-related effects on ECG parameters
Hematology	No test article-related effects on hematology parameters
Clinical chemistry	No test article-related effects on clinical chemistry parameter
Urinalysis	Blue/greenish blue discoloration of the urine at the MD and HD but not considered adverse.
Gross pathology	Blue coloration of the larger lymph nodes (mandibular, mesenteric) that was observed in males and females in the 10 mg/kg dose group. The color was attributable to the color of the test article.
Organ weights	No test article-related effects on organ weight
Histopathology	No test article-related effect on histopathology other than the coloration of the lymph nodes
Adequate battery: Yes	

Source: Reviewer's Table

Abbreviations: ECG = electrocardiogram

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Repeat Dose Toxicity Study in Rabbits

Study title/ number: A 7-Day Toxicity and Toxicokinetic Study of LUM015 Following Intravenous Administration in New Zealand White Rabbits with a 14-Day Recovery Phase / 51103-15-205

- No serious adverse effects were reported, and the test article-related findings were limited to a urine color change consistent with the color of the test article.
- Pegulicianine was not associated with any dose-related clinical findings, and all rabbits survived to scheduled necropsies.
- Based on the absence of any toxicologically relevant findings, the NOAEL was 15 mg/kg (the highest dose tested). Systemic exposure (C_{max} and AUC_{0-24}) at the NOAEL was 365 $\mu\text{g/mL}$ and 1,770 $\mu\text{g}\cdot\text{h/mL}$, respectively, for males and 356 $\mu\text{g/mL}$ and 1,930 $\mu\text{g}\cdot\text{h/mL}$, respectively, for females. On an AUC basis, the dose margin was 8.0-fold (males) and 8.7-fold (females) the proposed clinical dose of 1 mg/kg per administration.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 8. Methods for Study No.: 51103-15-205

Methods	Details
Dose and frequency of dosing	0 (vehicle), 15 mg/kg pegulicianine; daily for 7 days
Route of administration	Intravenous
Formulation/vehicle	Pegulicianine (Lot #: 117I1113, %purity: 96.9%) / normal saline
Species/strain	Rabbit/New Zealand White
Number/sex/group	4/sex/group for main study and 2/sex/group for recovery
Age	9 – 11 weeks at dosing
Satellite groups/ unique design	TK satellite, n=3/sex/group for pegulicianine
Deviation from study protocol affecting interpretation of results	No

Source: Reviewer's Table

Abbreviations: TK = toxicokinetic

Table 9. Observations and Results: Changes from Control (Study No.: 51103-15-205)

Parameters	Major Findings
Mortality	No mortality was reported. All animals survived until necropsy.
Clinical signs	No treatment related clinical signs reported in the treated animals. However, there was urine color change attributable to the color of the test article. No treatment-related effect on body temperature or heart rate.
Body weights	No test article-related change in body weight
Ophthalmoscopy	No test article-related change in ophthalmology parameters
Hematology	No test article-related change in hematology parameters
Clinical chemistry	No test article-related change in clinical chemistry
Urinalysis	Test article-related green to greenish-yellow discoloration of the urine; not considered adverse and absent in recovery animals.
Gross pathology	No test article-related change in gross pathology

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Parameters	Major Findings
Organ weights	No test article-related change in organ weight
Histopathology	No test article-related effect on histopathology
Adequate battery: Yes	

Source: Reviewer's Table

General Toxicology; Additional Studies

None.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: AMES TEST FRAGMENT 1 (QSY21-εAhx-Gly-Gly-Arg-OH, TFA Salt) / T64512002-GT

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, Fragment 1 at up to 600 µg/plate was not positive with any of the tester strains in either the absence or presence of S9 metabolic activation.
- Precipitate was observed at 500, 1600, and 5000 µg/plate. No cytotoxicity was observed at up to 5000 µg/plate.
- Fragment 1 was negative (non-mutagenic) in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Five histidine-dependent strains of Salmonella typhimurium (TA98, TA100, TA102, TA1535, and TA1537) in the absence and presence of Aroclor-induced rat liver microsome fraction (S9)

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: Fragment 1: In Vitro Chromosome Aberration Assay in Human Peripheral Blood Lymphocytes / 51106-18-835

Key Study Findings:

- Fragment 1 at doses up to and including 25 µg/mL did not result in any significant increases in cells with structural chromosomal aberrations in either the absence (up to 24 hours) or presence (up to 3 hours) of S9 metabolic activation.
- Based on the findings, Fragment 1 was negative for clastogenic potential in human peripheral blood lymphocytes under the conditions of the assay.

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GLP compliance: Yes

Test system: Cultured human peripheral blood lymphocytes in the absence (3 hours and 24 hours) and presence (3 hours) of β -naphthoflavone and phenobarbital-induced rat liver microsome fraction (S9)

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Micronucleus Assay in Mice / 51106-18-836

Key Study Findings:

- Fragment 1 at dose levels up to and including 11.24 mg/kg did not show any genotoxic activity in this in vivo test for induction of chromosomal damage (ratio of polychromatic erythrocytes to normochromatic erythrocytes and mean frequency of micronucleated polychromatic erythrocytes).
- Based on the findings, Fragment 1 was negative for genotoxic potential in the assay.

GLP compliance: Yes

Test system: CD-1 mice [ICR] (SPF); 7 to 8 weeks of age

Study is valid: Yes

Other Genetic Toxicity Studies

None.

Conclusion Based on Genotoxicity Studies

No genotoxic hazards were identified when pegulicianine Fragment 1 containing QSY21 was evaluated in the standard International Conference on Harmonization-compliant genotoxicity battery consisting of a bacterial reverse mutation assay, an in vitro clastogenicity assay conducted in human peripheral blood lymphocytes, and an in vivo mouse bone marrow micronucleus study.

5.5.3. Carcinogenicity

Studies examining the carcinogenic potential of pegulicianine have not been conducted and are not needed because pegulicianine will be administered as a single or infrequent dose and because of the negative findings in genotoxicity studies.

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5.5.4. Reproductive and Developmental Toxicology

No development and reproductive toxicology studies for pegulicianine were conducted or identified in the peer-reviewed scientific literature. The Applicant requested to omit the conduct of development and reproductive toxicology studies of pegulicianine. The Agency concluded that this request was justified because pegulicianine is an optical imaging agent with a short half-life (5 to 7 hours) that will be administered as a single or infrequent dose to patients with breast cancer (of whom 70 – 80% are past childbearing age) undergoing tumor resection. Moreover, the Agency considered that there would be comparatively minimal risk to reproductive health of the patient and/or the developing fetus compared to the known pregnancy risks and embryo-fetal toxicity associated with certain adjuvant therapy.

The waiver request was granted based on the proposed single-use indication, intended clinical population, and totality of nonclinical data that suggested pegulicianine would pose no risk to the developing fetus.

5.5.5. Other Toxicology Studies

Phototoxicity

Study Title/Number: Full Phototoxicity Test Report for the LUM Imaging System (b) (4) / TX0014rA

Study Objective: This non-GLP study was conducted to evaluate pegulicianine, proteolytic Fragments 1 – 3, Cy5, and nonfluorescent quencher QSY21 for phototoxicity by neutral red uptake (NRU) assay. Methylene Blue, Indocyanine Green, Rose Bengal, and Visudyne (verteporfin) were employed as controls. Absorbance extinction coefficients were determined for QSY21 carboxylic acid (36 μM), Cy5 mono acid (2.3 μM), and LUM015 Acetate (3.4 μM) analytes. Reactive oxygen species assays included 3'-(hydroxyphenyl) fluorescein and Singlet Oxygen Sensor Green assays.

Key Study Findings:

- Pegulicianine was negative for phototoxicity by NRU assay at 1 μM .
- Limited phototoxicity (15% cell death) was observed for Cy5 and QSY21 at 5 μM when incubated for more than 1 hour and 10 J cm^{-2} light (630 nm) or equivalent to 166 sec of exposure to imaging device excitation.
- Positive control Visudyne at 1 μM showed 80% cytotoxicity at 10 min and 95% at 1 hour.
- Minimal reactive oxygen species were observed by hydroxyphenyl fluorescein and Singlet Oxygen Sensor Green assays.

Conclusion: The results demonstrated that pegulicianine or its components are not likely to generate significant amounts of reactive species in vivo when exposed to the illumination from the LUM 2.6 Imaging Device at the employed parameters. It was also found that pegulicianine

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and its components did not have a bearing on cell viability for the NRU test. Thus, phototoxicity studies conducted using NRU and reactive oxygen species assays for pegulicianine and its components indicated it was unlikely to be phototoxic in vivo.

Impurity Evaluation

Impurities present in clinical lots of pegulicianine ([Table 10](#)) that exceeded qualification threshold levels per International Conference on Harmonization Q3A and Q3B were qualified in a 7-day repeat-dose toxicity study in rabbits (Study No. 51103-15-205). The toxicology qualifications of impurities/degradants above the thresholds were based on the NOAEL of 15 mg/kg dose level in rabbits.

Table 10. Impurity Acceptance Criteria in the Drug Substance and Drug Product

(b) (4)

The Applicant provided a scientific justification for not conducting genotoxicity assessment for impurities exceeding a qualification threshold of (b) (4)%. The justification provided was that the peptide linker of pegulicianine is cleaved proteolytically, resulting in three fragments with Fragment 1 containing the QSY21 non-fluorescent quencher, spacer, and peptide. Fragments 2 and 3 contain Cy5 and PEG is present only on Fragment 2. Fragments 2 and 3 and their components were not considered to have any genotoxic potential and Fragment 1 was evaluated by a complete battery of genotoxicity studies. The impurities present in the clinical lots of pegulicianine were therefore considered qualified and no additional evaluation was needed.

6. Clinical Pharmacology

6.1.Executive Summary

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 214511. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in [Table 11](#).

Table 11. Recommendations and Comments for NDA 214511

Review Topics	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is provided by Study CL0007 (see Section 6.3.2).
General dosing instructions	The recommended dose for pegulicianine is 1 mg/kg by IV injection (over 3 min) to be administered 2 to 6 hours prior to imaging.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The effects of moderate or severe renal impairment on pegulicianine or its fluorescent metabolites (Fragments 2 and 3) have not been evaluated.
Drug-drug interactions	No dedicated drug interaction study was conducted.
Labeling	The PK results were not included in the PI due to bioanalytical issues (see Section 16.3.1).
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

Source: FDA clinical pharmacology reviewer

Abbreviations: IV = intravenous, PI = prescribing information, PK = pharmacokinetic

Post-Marketing Requirement or Commitment

None.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Clinical Pharmacokinetics

Patients

Due to the lack of a validated PK assay, there are no PK data available in patients with cancer.

Healthy Subjects

Based on a validated PK assay in healthy subjects (HS), approximately dose-proportional increases in exposures for pegulicianine and Fragment 3 were observed from 0.5 to 4 mg/kg (Fragments 1 and 2 were not measured). The mean elimination half-lives (%CV) for pegulicianine and Fragment 3 are 5 h (14%) and 7 h (14%), respectively, following a single dose of 1 mg/kg pegulicianine in HS.

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Metabolism

Pegulicianine is cleaved by enzymes including cathepsins and matrix metalloproteases to the active metabolites Fragment 2 and Fragment 3. The pharmacokinetics of these active metabolites are unknown. Pegulicianine undergoes minimal hepatic metabolism *in vitro*.

Excretion

The pegulicianine excretion pathway in humans is unknown. Blue/green discoloration of urine (chromaturia) in patients receiving pegulicianine suggests that pegulicianine and/or its metabolites are excreted renally. Discoloration of urine resolved between 24 to 48 hours following pegulicianine administration in most patients (>90%).

Specific Populations

The effect of moderate or severe renal impairment on pegulicianine PK, safety, or efficacy has not been evaluated.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose for pegulicianine of 1 mg/kg by IV injection (over 3 min) administered 2 to 6 hours prior to imaging is approvable.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A general overview of pegulicianine absorption, distribution, metabolism, excretion, and clinical PK information is presented in [Table 12](#).

Table 12. ADME and Clinical PK Information for Pegulicianine

Parameter	Information
Physicochemical properties	
Chemical structure	Refer to Section 4.2

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Parameter	Information
Pharmacology	
Mechanism of action	Pegulicianine is a prodrug that is optically inactive when intact and produces a fluorescence signal after its peptide chain is cleaved by enzymes including cathepsins and matrix metalloproteases. The levels of these enzymes are higher 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 on a computer screen to show suspected tissue containing cancer within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery.
Active moieties	The enzymatic cleavage results in Fragment 2 and Fragment 3, which are optically active metabolites that emit fluorescence, as well as Fragment 1 containing the fluorescence quencher that keeps the intact molecule optically inactive. Fragment 2 and Fragment 3 absorb light in the visible light region with a peak absorption at 650 nm and fluoresce with a peak emission at 675 nm.
Imaging time window post-dose	In Study CL0007, 1 mg/kg pegulicianine was administered 2 to 6 hours prior to imaging time.
QT/QTc prolongation	The FDA QT-IRT review noted that pegulicianine did not prolong the QTc interval based on assessment of the ECG/PK data from QT Study CLP00201 and that the assessment can be used as a substitute for a thorough QT study.
General information	
Bioanalysis	Due to the lack of a validated PK assay, there are no PK data available in patients with cancer (see Section 16.3.1).
Healthy subjects vs. patients	Unknown.
Drug exposure at steady state following the therapeutic dosing regimen	N/A (indicated for single-dose administration).
Minimal effective dose or exposure	N/A.
Maximal tolerated dose or exposure	The maximum dose evaluated was 4 mg/kg. The MTD was not reached.
Dose proportionality	Approximately dose-proportional increases in pegulicianine and Fragment 3 exposures in HS (1 to 4 mg/kg).
Accumulation	N/A (indicated for single-dose administration).
Variability	%CV for C _{max} and AUC ranged from 10 – 25% (pegulicianine) and 7 – 34% (Fragment 3) following 0.5 to 4.0 mg/kg administration in HS.
Distribution	
Volume of distribution	The mean (%CV) pegulicianine volume of distribution is 57 mL/kg (15%) following 1 mg/kg pegulicianine in HS.
Plasma protein binding	Not evaluated.
Blood to plasma ratio	Not evaluated.
Elimination	
Half-life	The mean (%CV) elimination half-lives for pegulicianine and Fragment 3 are approximately 5 h (14%) and 7 h (14%), respectively, following 1 mg/kg pegulicianine in HS.
Clearance	The mean (%CV) pegulicianine clearance is 9 mL/h/kg (24%) following 1 mg/kg pegulicianine in HS.

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Parameter	Information
Metabolism	
Primary metabolic pathway(s)	Pegulicianine is cleaved by cathepsins and matrix metalloproteases to the active fluorescent metabolites known as Fragment 2 and Fragment 3. The PK of these active fluorescent metabolites are unknown. Pegulicianine undergoes minimal hepatic metabolism in vitro.
Inhibitor/inducer	Pegulicianine is not an inhibitor of CYP enzymes. Induction potential of pegulicianine has not been evaluated. Inhibition and induction potential of Fragment 2 and Fragment 3 have also not been evaluated.
Excretion	
Primary excretion pathways (% dose) ±SD	Although a mass balance study has not been performed, a major elimination pathway for pegulicianine and its metabolites appears to be renal, as blue/green discoloration of urine (reflecting the presence of the similarly colored parent drug) has been observed in almost all patients who received pegulicianine.

Source: FDA clinical pharmacology reviewer

Abbreviations: ADME = absorption, distribution, metabolism, excretion, AUC, area under the curve, C_{max} = maximum plasma concentration; CV = coefficient of variation, CYP = cytochrome P450, DVS = direct visualization system, ECG = electrocardiogram, HS = healthy subjects, IRT = Interdisciplinary Review Team, MTD = maximum tolerated dose, N/A = not applicable, PK = pharmacokinetics, QT = QT interval, QTc = corrected QT interval

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. Primary evidence of effectiveness was obtained from the Applicant's pivotal study CL0007.

Study CL0007 was a prospective, multi-center, 2-arm, randomized study to evaluate the safety and efficacy of LUMISIGHT in identifying residual cancer in the lumpectomy cavity of patients with breast cancer (N=406: 357 randomized to imaging arm, 35 randomized to control arm, 14 withdrawals). Eligible patients were injected with LUMISIGHT at a dose of 1.0 mg/kg at 2 to 6 hours prior to imaging. The patients received SoC BCS where the main specimen and selective or comprehensive shaves were removed by the surgeon. After the SoC BCS was completed, randomization to study arms at a 10:1 ratio (Lumicell DVS imaging arm : control no imaging arm) was revealed. Patients who were randomized to the Lumicell DVS imaging arm underwent image-guided tissue resection (image-guided shaves), while patients who were randomized to the control arm had no further resection. Following surgery, all resected specimens were sent to the pathology laboratory at each site for margin assessment per SoC.

The efficacy results met the pre-specified performance goals for removal of residual cancer (27/357 (7.6%), 95% CI: 5.0%, 11%; performance goal >3%) and specificity (1940/2277 (87%), 95% CI: 85%, 88%; performance goal >60%) but not for sensitivity (34/69 (49%), 95% CI: 36%, 62%; performance goal >40%). The most common AE was chromaturia. For detailed efficacy and safety results, refer to Statistical and Clinical Section [8](#).

Imaging Time Selection

The administration of LUMISIGHT 2 to 6 hours prior to imaging was primarily based on the results from the Applicant's phase 1 study DUK1-12-137.

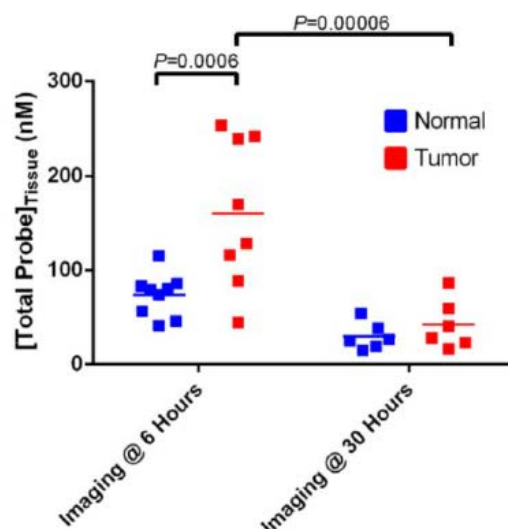
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Study DUK1-12-137 was a single-center, open-label study that evaluated LUMISIGHT in adult patients with soft tissue sarcoma or breast cancer (N=15, 12 with sarcoma, 3 with breast cancer). Single doses of pegulicianine were administered prior to imaging during resection surgery by cohort (n=3/cohort). The first and second cohort evaluated doses of 0.5 and 1.0 mg/kg administered approximately 30 hours prior to imaging. PK data from the first two cohorts revealed that pegulicianine clearance in humans was faster than expected, thus the next three cohorts evaluated doses of 0.5, 1.0, and 1.5 mg/kg administered approximately 6 hours prior to imaging.

As shown in [Figure 9](#), the concentration of total fluorescent probe (nM) in tumor tissues was significantly higher than in normal tissues (e.g., muscle, fat). Additionally, imaging at 6 hours post-injection showed higher overall absolute tissue fluorescence and higher tumor:normal tissue ratio (T:N) contrast compared to imaging at 30 hours post-injection.

Figure 9. Total Fluorescent Probe Per Normal or Tumor Tissue vs. Imaging Time (Study DUK1-12-137, Whitley 2016)



Source: Figure S3 in Whitley 2016¹. Total probe concentration determined for 15 normal and 14 tumor tissue samples from human subjects equals sum of pegulicianine, fragment 2 and fragment 3 concentrations per sample

Based on these results, the 6-hour timepoint was selected as optimal by the Applicant. The Applicant also expanded the imaging window to 2 to 6 hours post-injection to accommodate pre-surgery workflows and patient management for evaluation in their next study (IDE Feasibility Phase A Study). Imaging times within 2 to 6 hours were further evaluated in Study CL0007, as described below.

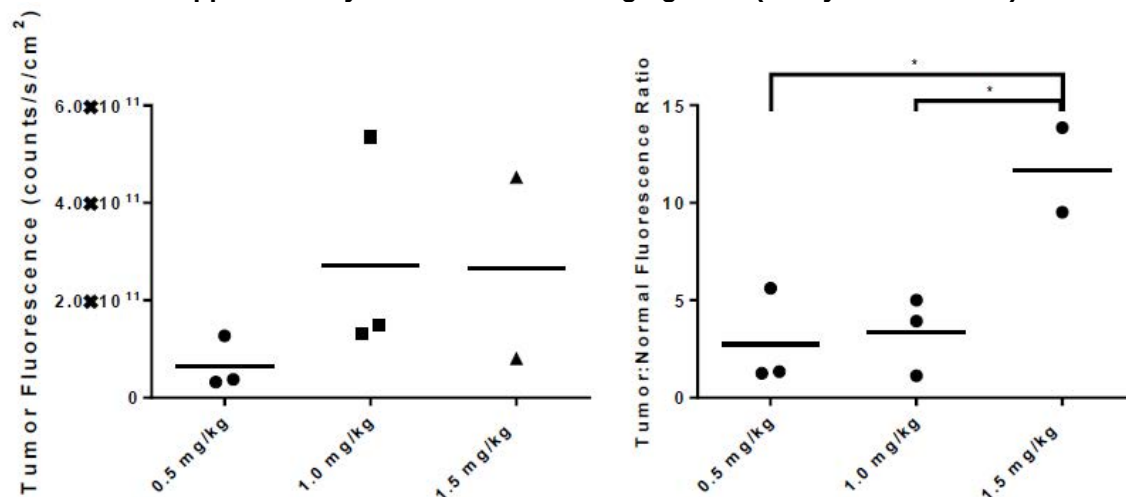
Dose Selection

Dose-response data showed that 1.5 mg/kg (administered approximately 6 hours prior to imaging) resulted in the highest T:N fluorescence ([Figure 10](#)). LUMISIGHT was well tolerated with discoloration of urine as the primary drug-related AE reported.

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Figure 10. Tumor Fluorescence (Left) and T:N Fluorescence (Right) for 0.5 to 1.5 mg/kg Administered Approximately 6 Hours Prior to Imaging Time (Study DUK1-12-137)



Source: Figure 11-4 From Study DUK1-12-137 CSR

Abbreviations: CSR = clinical study report, T:N = tumor-to-normal tissue ratio

While the dose-response data showed that 1.5 mg/kg resulted in higher T:N fluorescence compared to 0.5 and 1.5 mg/kg ([Figure 10](#)), the Applicant selected the lower doses of 0.5 and 1.0 mg/kg to evaluate in their next clinical study (IDE Feasibility Phase A Study).

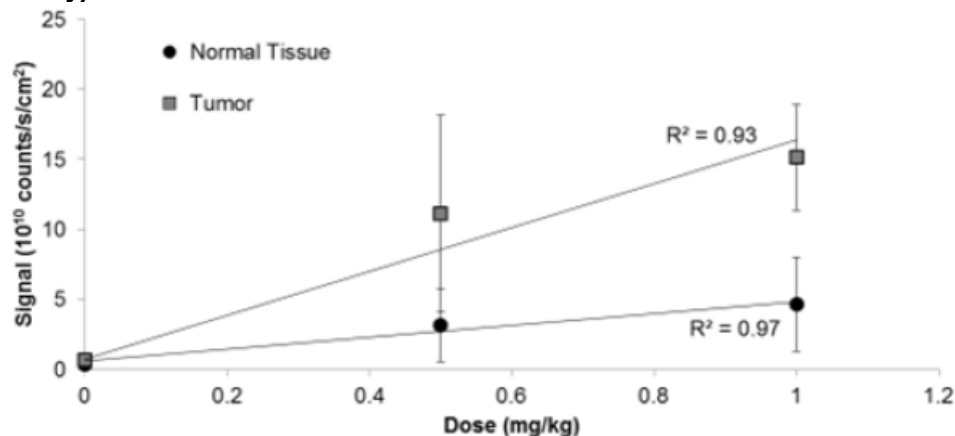
IDE Feasibility Phase A was an open-label study that evaluated LUMISIGHT in adult patients undergoing lumpectomy for primary breast cancer (N=15). Five patients were enrolled in each of three arms: no imaging agent (Arm 1), 0.5 mg/kg (Arm 2), and 1.0 mg/kg (Arm 3). LUMISIGHT was administered 2 to 6 hours prior to surgery.

The results suggested that the fluorescence signal in the primary breast cancer increased proportionally with the dose in both normal and tumor tissues ([Figure 11](#)). The Applicant conducted dose-response modeling of the T:N fluorescence ratio and %CV vs. dose ([Figure 12](#)), which they conclude implies that doses above 1.0 mg/kg may not improve the T:N ratio or decrease the variability in the fluorescence signals. However, the Applicant's interpretation is not supported by the data. [Figure 11](#) indicates a monotonic increase in response to dose. Since there was no dosing group at 1.5 mg/kg, it cannot be determined whether the response to the increased dose would increase or plateau at the same level as the 1 mg/kg dose ([Figure 12](#)). The results of DUK1-12-137 indicated that higher T:N ratios resulted at the 1.5 mg/kg dose (3-4 fold higher as compared to 0.5 or 1.0 mg/kg) ([Figure 10](#)), Therefore, it is unclear whether a higher dose of pegulicianine would increase the T:N signal ratio.

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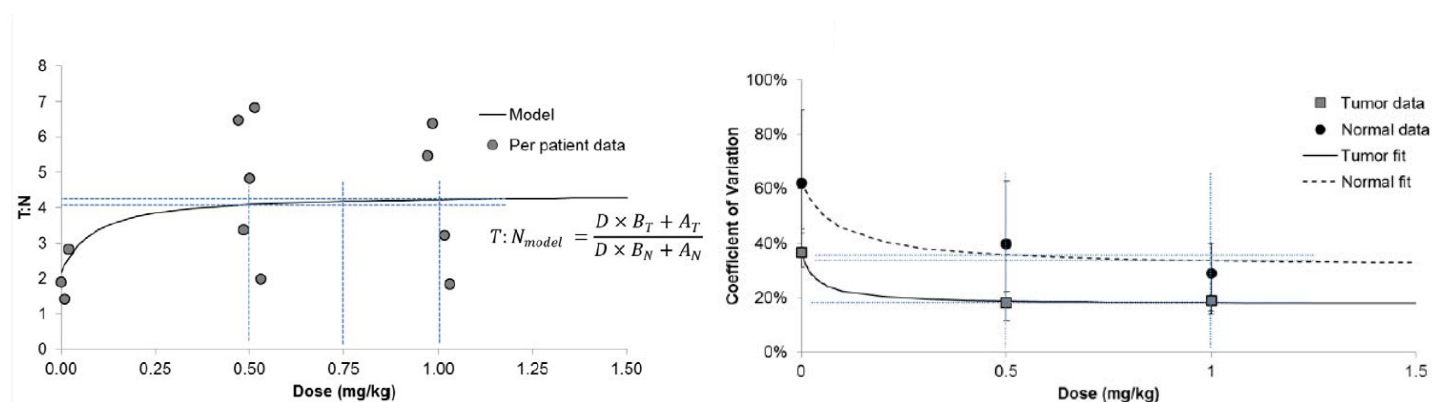
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Figure 11. Fluorescence Signal in Normal and Tumor Tissue vs. Dose (IDE Feasibility Phase A Study)



Source: Figure 6 From Applicant's 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: IDE = investigational device exemptions

Figure 12. Applicant's Dose-Response Modeling for T:N Fluorescence Ratio (Left) and %CV (Right) vs. Dose



Source: Figures 7 and 8 From Applicant's 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: CV= coefficient of variation, T:N = tumor:normal

Pivotal Study

An analysis of efficacy endpoints (removal of residual cancer, sensitivity, specificity) versus imaging time (2-3, 3-4, 4-5, 5-6 h post-administration of pegulicianine) was conducted. The analysis did not reveal major differences in the co-primary efficacy endpoints for the analyzed time windows ([Table 13](#)). These data support the proposed imaging time.

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Table 13. Efficacy Endpoints vs. Imaging Time from Study CL0007

First Imaging Time Post-administration of Pegulicianine	Removal of Residual Cancer ²	Sensitivity (tissue level) ³	Specificity (tissue level) ³
2 - 3 Hours	n = 80 patients 10% (8/80) 95% CI [4.4%, 18.8%]	44.9% (9/21) 95% CI [24.3%, 67.5%]	87.9% (437/507) 95% CI [83.4%, 91.3%]
3 - 4 Hours	n = 153 patients 7.2% (11/153) 95% CI [3.6%, 12.5%]	42.2% (15/33) 95% CI [25.2%, 61.4%]	87.5% (823/955) 95% CI [84.2%, 90.2%]
4 - 5 Hours	n = 88 patients 6.8% (6/88) 95% CI [2.5%, 14.3%]	50.0% (6/9) 95% CI [49.996%, 50.011%]	85.7% (487/575) 95% CI [81.4%, 89.1%]
5 - 6 Hours ¹	n = 36 patients 5.6% (2/36) 95% CI [0.7%, 18.7%]	50% (4/6) 95% CI [12.3%, 87.7%]	81.5% (193/240) 95% CI [74.6%, 86.8%]
¹ Group 5 - 6 hours included 8 patients having the first imaging time more than 6 hour but less than 7 hours post-administration of pegulicianine			
² Binomial estimation			
³ Generalized Estimating Equation (GEE) method to account for intra-patient correlations.			

Source: Table 3 from Applicant's Response to Clinical Pharmacology information request (dated 9-26-23)

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The 1.0 mg/kg dose achieved the pivotal study endpoint for specificity, although it was slightly below the pre-specified threshold for sensitivity and is considered appropriate. It remains unclear whether a higher dose might enhance LUMISIGHT imaging.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No. LUMISIGHT has been evaluated in patients with cancer and HS with mild RI (renal impairment), as shown in [Table 14](#). There does not appear to be a clinically relevant effect of mild RI on pegulicianine or Fragment 3 pharmacokinetics in patients with cancer (based on a non-validated PK assay ([Figure 13](#))) and HS (based on a validated PK assay ([Figure 14](#))).

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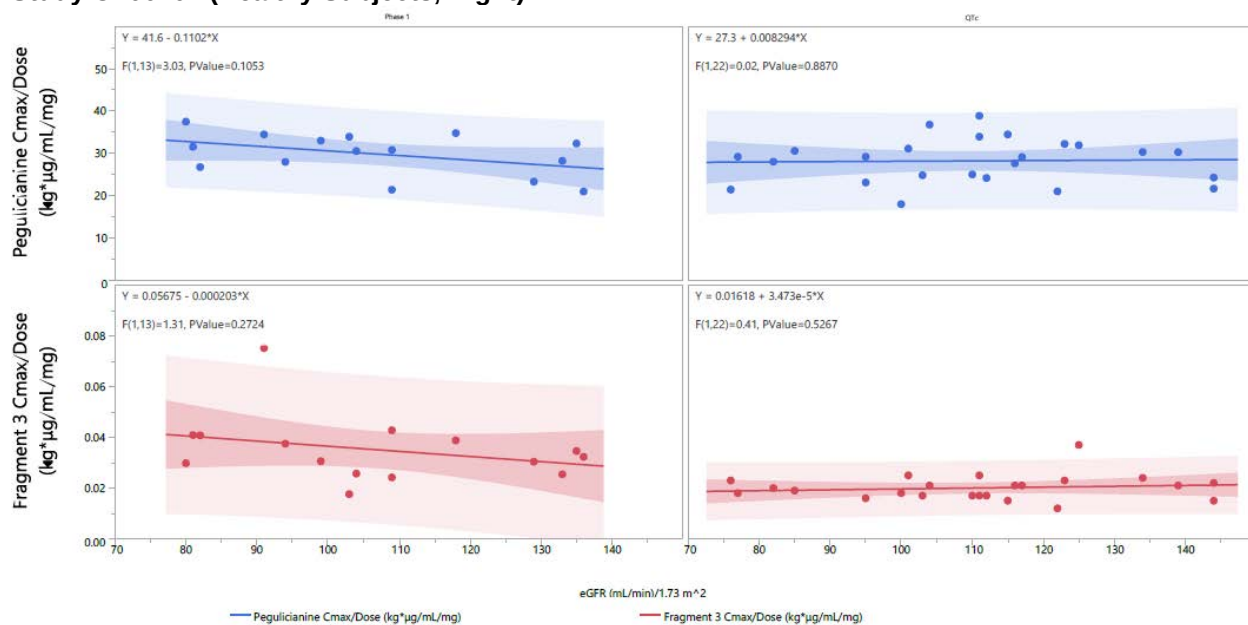
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Table 14. Number of Subjects by Renal Function Category in Phase 1 Study DUK1-12-137 and QTc Study CLP00201

Population and Study	Normal Renal Function ($\text{eGFR}^a \geq 90 \text{ mL/min}$)	Mild Renal Impairment ($60 \text{ mL/min} \geq \text{eGFR}^a < 90 \text{ mL/min}$)
Subjects with cancer in the Phase 1 Study	12 (80%)	3 (20%)
Healthy subjects in the QTc Study	20 (83%)	4 (17%)
Combined pharmacokinetic population (n = 39)	32 (82%)	7 (18%)

Source: Table 13 from Applicant's 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: eGFR = estimated glomerular filtration rate, QTc = corrected QT interval

Figure 13. C_{max} /Dose vs. eGFR in Phase 1 Study DUK1-12-137 (Patients with Cancer, Left) and QTc Study CL00201 (Healthy Subjects, Right)

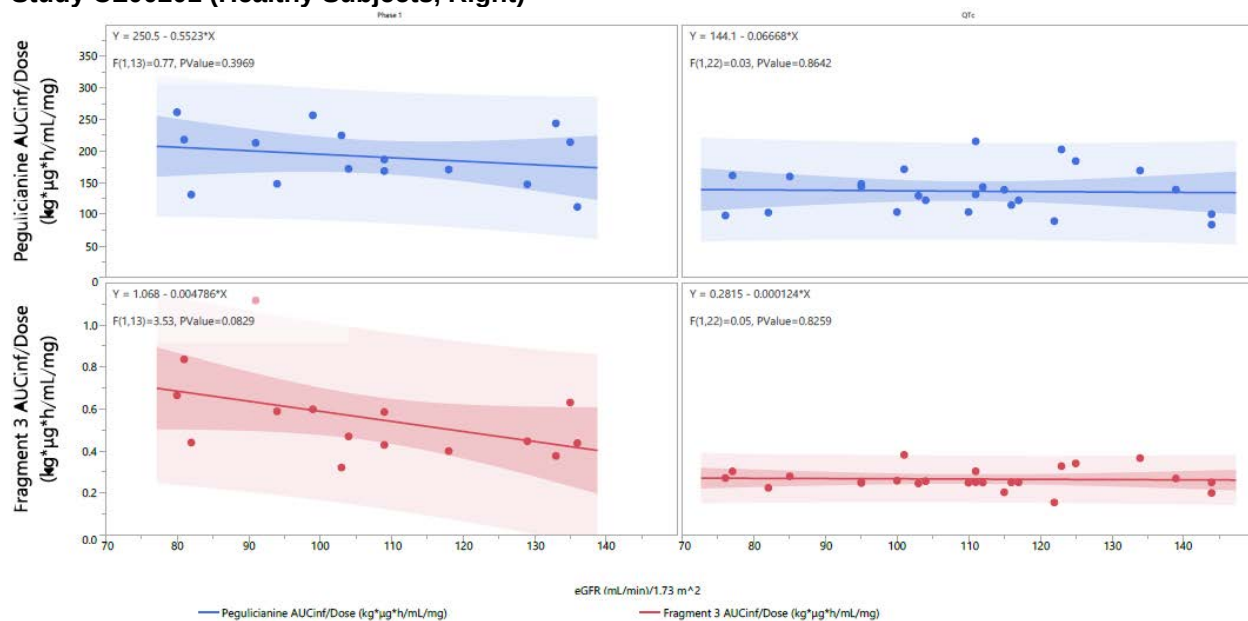


Source: Figure 17 from Applicant's 2.7.2 Summary of Clinical Pharmacology Studies
Abbreviations: C_{max} = maximum plasma concentration, eGFR = estimated glomerular filtration rate, QTc = corrected QT interval

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Figure 14. AUC/Dose vs. eGFR in Phase 1 Study DUK1-12-137 (Patients with Cancer, Left) and QTc Study CL00201 (Healthy Subjects, Right)



Source: Figure 18 from Applicant's 2.7.2 Summary of Clinical Pharmacology Studies

Abbreviations: AUC = area under the curve, AUC_{0-inf} = area under the curve from 0 to infinity, eGFR = estimated glomerular filtration rate, QTc = corrected QT interval

The PI notes the following:

Mild renal impairment (RI) does not appear to have a clinically relevant effect on the pharmacokinetics, safety, and efficacy of pegulicianine and fragment 3 (fragment 2 was not measured appropriately). The effect of moderate or severe RI on the pharmacokinetics, safety, and activity of pegulicianine, fragment 2, and fragment 3 has not been evaluated.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

No.

Question on Clinically Relevant Specifications (TBD)?

No.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 15. Table of Clinical Studies

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries/ Status
<i>Controlled Studies to Support Efficacy and Safety</i>						
CL0007	2-arm, randomized, intra-patient comparison	1 mg/kg iv	Ratio of patients with cancer found in at least 1 LUMISIGHT-guided shave; Tissue-level sensitivity and specificity	406	Adults with breast cancer undergoing BCS	14 (U.S.)/ completed
<i>Additional Studies to Support Efficacy and Safety</i>						
CL0006	Nonrandomized	1 mg/kg iv	Refine and verify the tumor detection algorithm	234	Adults with breast cancer undergoing BCS	16 (U.S.)/ completed
<i>Additional Studies to Support Safety</i>						
DUK1-12-137	Nonrandomized	0.5, 1, 1.5 mg/kg iv	Determine phase 2 dose	15	Adults with soft tissue sarcoma or breast cancer	1 (U.S.)/ completed
LUM-015/2.6-001	Nonrandomized	0.5, 1 mg/kg iv	Determine phase 3 dose; evaluate the detection algorithm for identifying residual cancer in the tumor bed	55	Adults with breast cancer	1 (U.S.)/ completed
CLP0008	2-arm, randomized	1 mg/kg	Develop and validate tumor detection algorithms in patients with breast cancer receiving neoadjuvant therapy	11	Adults with breast cancer who have received neoadjuvant therapy	Multiple/ ongoing

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Trial Identity	Trial Design	Regimen/ Schedule/ Route	Key Objectives	Sample Size	Study Population	No. of Centers and Countries/ Status
CL0005	Nonrandomized	0.5, 1 mg/kg iv	Assess the initial safety and activity of LUMISIGHT in prostate cancer using ex vivo imaging with the Lumicell DVS	6	Adults with prostate cancer	1 (U.S.)/ terminated early
CL0003	Nonrandomized	0.5, 1, 1.5 mg/kg iv	Assess the initial safety and activity of LUMISIGHT in gastrointestinal cancers using ex vivo imaging with the Lumicell DVS	38	Adults with gastrointestinal cancers	1 (U.S.)/ ongoing
CLP00201	Randomized, double-blind, placebo controlled	0.5, 1, 2, 4 mg/kg iv	Evaluate the effects of LUMISIGHT on cardiac repolarization	24	Healthy subjects aged 18 to 59 years	1 (U.S.)/ completed

Source: Adapted from Table 1 of the Integrated Summary of Safety

Abbreviations: BCS = breast conserving surgery, DVS = direct visualization system, U.S. = United States

7.2.Review Strategy

Primary evidence of effectiveness of LUMISIGHT was provided in study CL0007. Study CL0006 was a source of confirmatory evidence. The remaining studies listed in [Table 15](#) were reviewed for safety only.

8. Statistical and Clinical Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. CL0007

8.1.1.1. Study Design

Overview and Objectives

CL0007 was a prospective, multicenter study to evaluate the safety and efficacy of the optical imaging agent LUMISIGHT used with the Lumicell DVS to identify and guide the removal of residual cancer in the lumpectomy cavity of patients with breast cancer. The study used a two-arm, randomized, intra-patient control design to reduce the risk of surgical bias and minimize variability due to study-subject and operating-surgeon factors. Surgeons were unaware of the randomization status for a specific patient until the SoC lumpectomy was completed.

Trial Design

CL0007 enrolled adults who had primary invasive breast cancer with or without DCIS or had DCIS only. All patients were required to be scheduled for a lumpectomy whereas, neoadjuvant therapy (chemotherapy, hormonal therapy, or radiotherapy) was not permitted. 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 15](#). 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

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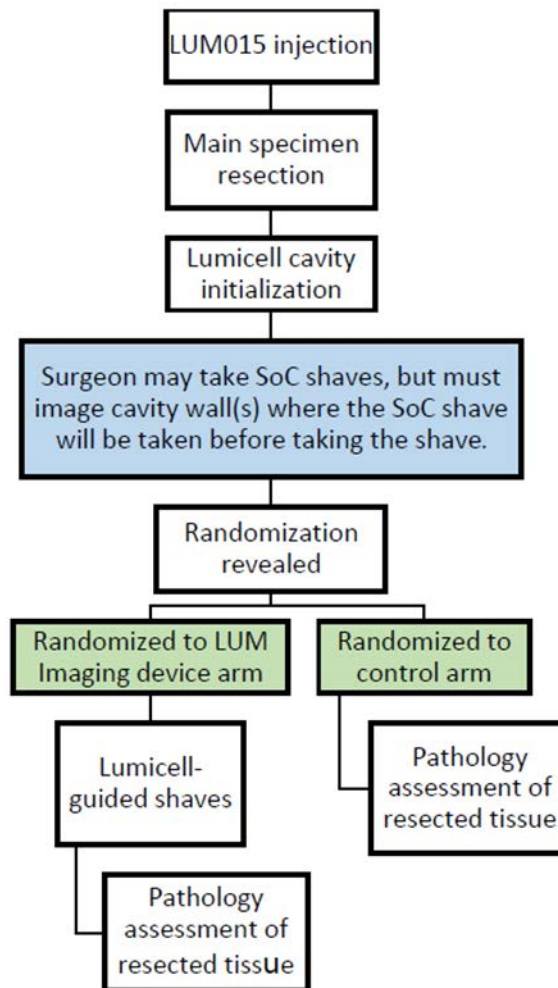
randomization, received 1 mg/kg LUMISIGHT intravenously injected over 3 minutes, 2 to 6 hours prior to surgery. Patients then proceeded to their planned SoC BCS. The BCS consisted of removal of the main specimen, optionally followed by cavity shaves. SoC shaves could be selective, intended to remove 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.

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Figure 15. 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.

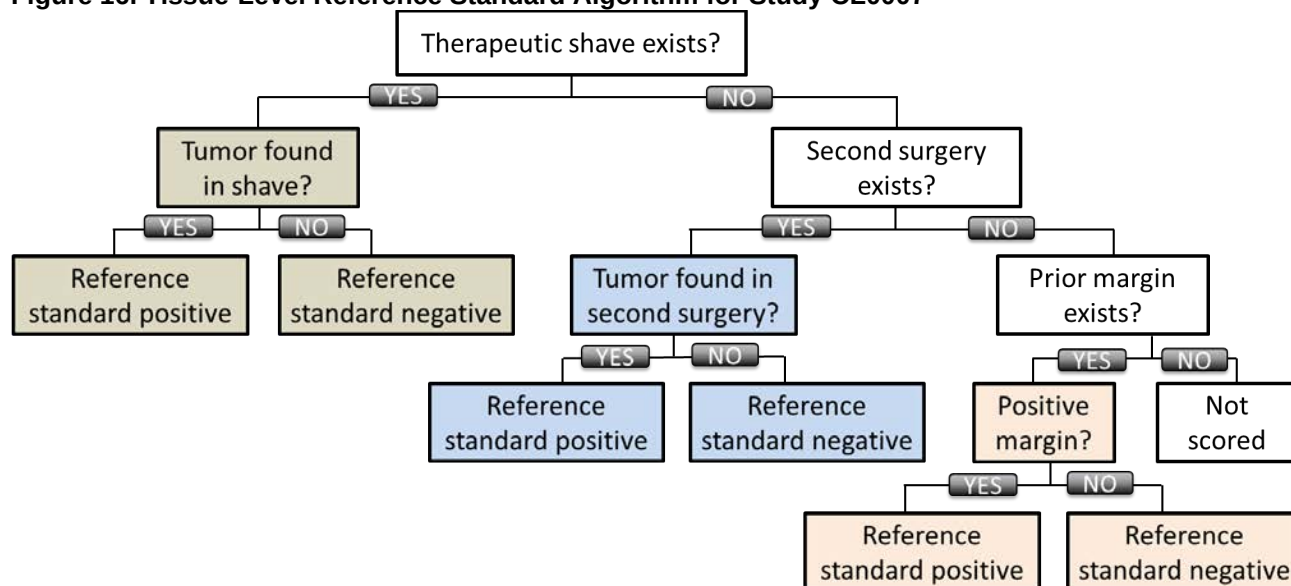
After BCS, patients were evaluated until the investigator determined that no additional surgery was required. If follow up surgery was performed, the nature of the surgery and results of local histopathology assessments were collected, including orientation-level margin status as available.

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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 16](#). 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 16. 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

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version 2.0 Breast Conserving Therapy Module was used. The survey consists of a pre-surgery questionnaire including 4 questions and a post-surgery questionnaire including 11 questions as described in [Table 16](#). For each question, the patient responded using a 4-level scale as follows: 1 = Very Dissatisfied; 2 = Somewhat Dissatisfied; 3 = Somewhat Satisfied; 4 = Very Satisfied.

Table 16. BREAST-Q Survey Items Used in CL0007

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

Source: Table 1 of Addendum to CL0007 Clinical Study Report

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 17](#))
- Tissue-level specificity ([Figure 17](#))

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Figure 17. Formulas for Tissue-Level Sensitivity and Specificity

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

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

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 of greatest interest for this review 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 and 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 Applicant defined the following populations for analysis.

- Safety: All patients who received LUMISIGHT
- Modified intent-to-treat (mITT): All patients in the safety population except those who could not be imaged with the Lumicell DVS
- Per-protocol: All patients in the mITT population who completed all study evaluations and had no major protocol deviations

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The mITT population was used for the primary efficacy analysis. Note that the safety population includes patients from both the device arm and the control arm, while the other populations exclude patients in the control arm.

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.

Protocol Amendments

The major protocol amendments are summarized in [Table 17](#).

Table 17. Study CL0007 Protocol Amendments

Protocol CL0007 Revision Number (Revision Date)	Purpose	Number (%) of Patients Enrolled Under Protocol Version
CL0007r01 to CL0007r05	Initial versions of the protocol not released to clinical sites. These were used to discuss the study design with FDA.	0
CL0007r06 (29 July 2019)	Initial version to start enrollment, sample size of 170 expected	196 (48%)
CL0007r07 (30 October 2020)	Changed study power calculation and endpoints in study protocol and statistical analysis plan; event-driven study; increased maximum number of patients to 350; expanded time for collection of patient reported outcome data from 3 months to 6 months	154 (38%)
CL0007r08 (07 April 2021)	Increased maximum number of patients to 450; clarifications of endpoints and updates to statistical analysis plan	56 (14%)

Source: Adapted from CL0007 Clinical Study Report Table 10

These protocol amendments did not affect the efficacy or safety evaluation of this NDA.

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8.1.1.2. Study Results

Compliance with Good Clinical Practice

The Applicant attested that the study was designed, conducted, and reported in compliance with Good Clinical Practice (GCP).

Financial Disclosure

The Applicant provided the complete list of investigators and certified that they have not entered into any financial arrangement with the listed clinical investigators.

Patient Disposition

A total of 490 patients provided informed consent ([Table 18](#)). 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. This included 7 patients withdrawn due to AEs, 2 due to device issues, 1 because the surgical incision was too small for the device, 3 who had blue dye injection, and 1 patient who 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 18. Patient Disposition in CL0007

Disposition	Number (%) of Patients
Patients with informed consent form signed	490 (100%)
Screen failures	84 (17%)
Patients having LUMISIGHT injected (Safety Population)	406 (83%)
Patients withdrawn after the injection but prior to randomization	14 (3%)
Patients randomized to the device arm (mITT Population)	357 (73%)
Patients in device arm withdrawn before completing Lumicell DVS imaging	1 (<1%)
Patients completed with Lumicell DVS imaging	356 (73%)
Patients in the per-protocol population	347 (71%)
Patients randomized to control arm	35 (7%)

Source: Adapted from Table 11 from CL0007 Clinical Study Report.

Abbreviations: DVS = direct visualization system, mITT = modified intent-to-treat

Protocol Violations/Deviations

A total of 135 protocol deviations were documented ([Table 19](#)).

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Table 19. Summary of Protocol Deviations in CL0007 by Deviation Type

Deviation Type	Protocol Deviations n (%)	Major Deviations n (%)	Patients with Protocol Deviations n (%)
Consent procedures	4 (3%)	2 (1%)	4 (5%)
Inclusion / exclusion criteria	7 (5%)	7 (5%)	7 (8%)
Laboratory assessments/ procedures	38 (28%)	18 (13%)	38 (45%)
Study procedures	36 (27%)	29 (21%)	33 (39%)
Temperature excursion	26 (19%)	0	0
Visit schedule / interval	20 (15%)	9 (7%)	20 (24%)
Other	4 (3%)	0	1 (1%)
Total	135 (100%)	65 (48%)	85 (100%)

Source: Adapted from Table 13 from CL0007 Clinical Study Report.

Four patients with protocol deviations were excluded from the mITT population due to enrollment criteria not being met. These patients were not imaged with Lumicell DVS.

- Three patients received a blue dye for lymphatic mapping prior to imaging with the Lumicell DVS.
- One patient received LUMISIGHT but prior to surgery was found to have had prior surgery on the ipsilateral breast.

Ten additional patients had protocol deviations resulting in exclusion from the per-protocol population.

- Eight patients were imaged more than 6 hours after injection with LUMISIGHT.
- Two patients had at least one image that was not saved.

The maximum time between imaging and LUMISIGHT administration was approximately 6 hours, 37 minutes. This amount of delay is likely to occur in routine use of the product, and the clinical team agrees with the Applicant that these patients should be included in the mITT population. For the 2 patients who had incomplete saving of images, 1 was missing a single image, and the images that were saved were included in the tissue-level analyses of the mITT population. The other patient had Lumicell DVS imaging but no images saved and was therefore included in the patient-level endpoints but not the tissue-level endpoints.

Fourteen patients had protocol deviations considered important by the Applicant that were related to imaging procedures or removal of shaves. Three patients, including 2 patients in the device arm, had at least one SoC shave taken after randomization was revealed. In these patients, the SoC margin evaluation for the study endpoints did not include those SoC shaves, however, those SoC shaves would have not affected the final margin as no cancer was detected in the shaves and the SoC margins before the shaves were all negative. Two therapeutic shaves in two patients in the mITT population did not have images saved. These shaves were removed from the primary endpoint calculation of sensitivity and specificity but were included for the final margin evaluation. Additionally, one SoC image did not have a shave associated with it and

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was removed from the secondary evaluation of tissue-level sensitivity and specificity among SoC shaves. Nine SoC shaves in eight patients did not have images saved in the device arm. These shaves were also removed from the secondary tissue-level sensitivity and specificity evaluation. However, these SoC shaves were included in the SoC margin evaluation.

The Clinical team deems that the protocol deviation in this study were unlikely to have a significant impact on efficacy or safety analyses.

Table of Demographic Characteristics

Patient demographics are presented in [Table 20](#). Overall, demographic characteristics of the enrolled patients were generally representative of the US population of newly diagnosed patients with breast cancer. The median age of 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 20. 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

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Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

As shown in [Table 21](#), 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 21. 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)
<i>Tumor histology (biopsy and/or main lumpectomy specimen)</i>			
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
<i>Preoperative lymph node status</i>			
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 22](#) 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 61,309 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 the aggressive nature of triple negative cancer resulting in more advanced disease at presentation that was less often amenable to BCS without preoperative systemic therapy.

Table 22. Tumor Receptor Status in CL0007

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

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Characteristic	Safety Analysis Population (N=406)	Modified Intent-to-Treat Population (N=357)	Control Population (N=35)
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.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

LUMISIGHT was administered by study personnel and treatment compliance is not applicable.

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%. Note that while this endpoint was named based on removal of cancer, we consider it to be a diagnostic, rather than therapeutic, measure of cancer detection in this setting where detected cancer is usually amenable to resection and where complete removal of cancer was not necessary for a patient to be evaluated for the endpoint.

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 23](#), the tissue-level sensitivity was 49% (34/69; 95% CI: 36%, 62%) and tissue-level specificity was 87% (1940/2277; 95% CI: 85%, 88%). Sensitivity did not meet its performance goal of 40%, while specificity exceeded its performance goal of 60%.

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Table 23. Tissue-Level Performance of LUMISIGHT for Detection of Residual Breast Cancer in the Lumpectomy Cavity

	Reference Standard		Total
	Positive	Negative	
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 2,346 tissues were evaluated among the patients in the mITT population. The distribution for each component of the composite reference standard is shown in [Table 24](#). 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 24. Use of the Components of the Reference Standard

Hierarchical Assessment	Total	Contribution From Therapeutic Shaves n (%)	Contribution From Second Surgeries n (%)	Contribution From Prior Margin n (%)
All tissues	2346	365 (16%)	68 (3%)	1913 (81%)
Truth standard positives	69	34 (49%)	24 (35%)	11 (16%)
Truth 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% (95% CI: 6%, 13%). 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%).

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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 25](#). 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 25. 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 26](#)) 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 26. Primary Endpoint Results by Types of Standard of Care Procedure

Parameter	All	Comprehensive	Selective Having SoC Shave	Selective with No SoC Shave
Number of patients	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.

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Tissue-level sensitivity and specificity by tumor histology type are presented in [Table 27](#). The number of reference standard positive tissues was too small for robust comparison of sensitivity between tumor types, though there may be a trend to slightly lower sensitivity in patients with DCIS only. Specificity trended lower for DCIS only or IDC+DCIS than IDC alone. The clinical significance of this observation is unclear.

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Table 27. Tissue-Level Performance by Tumor Histology Type

Parameter	All	DCIS	IDC	IDC+DCIS	IDC+ILC+ DCIS	ILC+DCIS
Number of 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

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Subgroup analyses of the 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.

Data Quality and Integrity

FDA OSI audits of the Applicant and representative clinical study sites revealed no significant unresolved GCP deviations.

Efficacy Results – Secondary and Other Relevant Endpoints

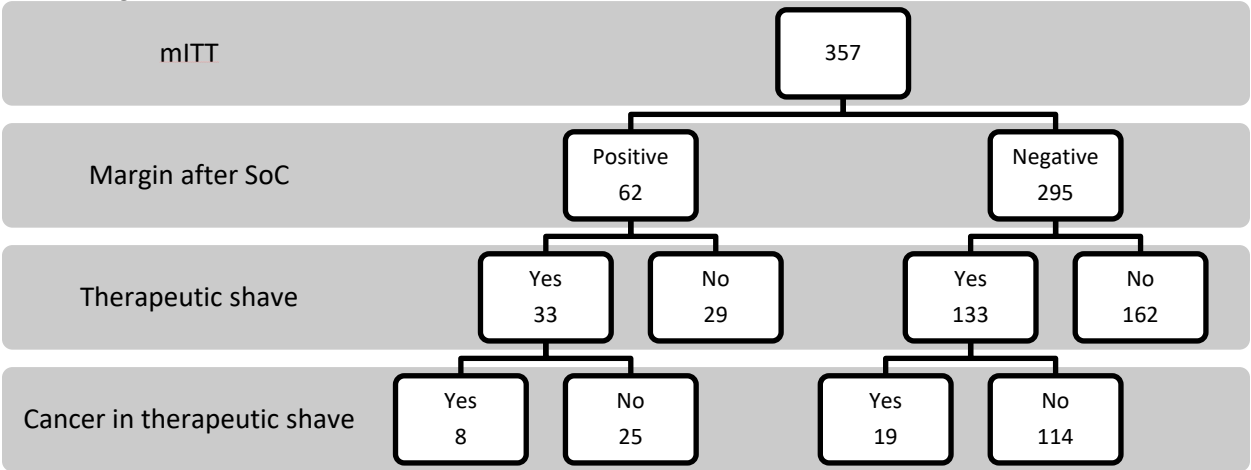
Among the 357 patients in the mITT Population, 62 (17%) had positive margins after the SoC surgery, i.e., before LUMISIGHT-guided intervention. In 10 of these 62 patients (16%; 95% CI: 7%, 25%), LUMISIGHT fluorescence was found in the cavity matching all orientations with positive margins. Nine of these patients (15% of patients with positive margins after SoC surgery [95% CI: 6%, 23%], 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 18](#), 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

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



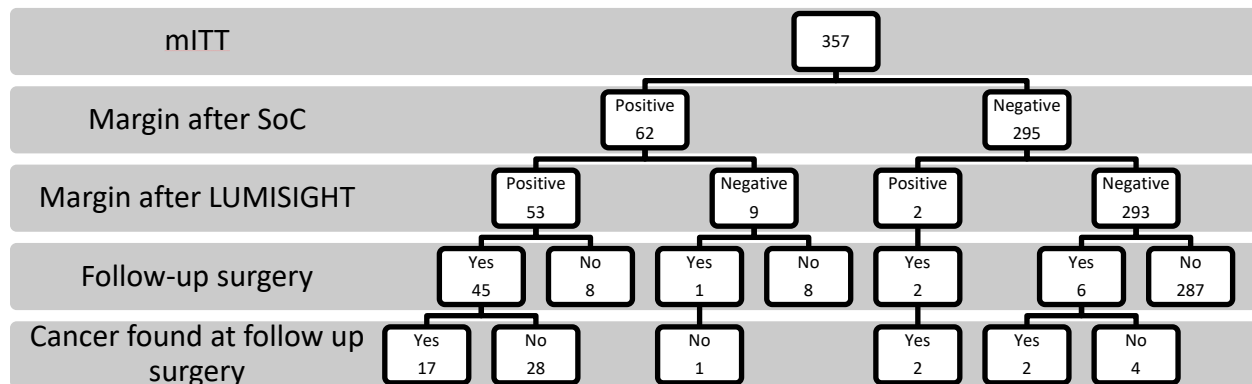
Source: FDA clinical reviewer
Abbreviations: mITT = modified intent-to-treat, SoC = standard of care

A total of 47 patients (13%) in the mITT population were recommended for and underwent second surgeries due to final positive margins after completion of BCS, including LUMISIGHT-guided therapeutic shaves, and an additional 7 patients had second surgeries for other reasons. The rate of cancer found in second 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 19](#)). 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. Because the clinical significance of removing cancer in patients with negative margins is unclear, it is reassuring that additional cancer was found at follow up surgery in both of these patients.

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Figure 19. 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, 87% versus 66% (Table 28). 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 28. 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.

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Abbreviations: SoC = standard of care.

Patient-level sensitivity and specificity analyses were performed based on the tissue-level results ([Table 29](#)). 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 8% (95% CI: 5%, 11%) and the fraction of patients who had at least one FP tissue was 43% (95% CI: 38%, 49%). 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 19% (95% CI: 4%, 33%) and the fraction of patients who had at least one FP tissue was 59% (95% CI: 41%, 78%). In the mITT population, 39% (95% CI: 34%, 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 29. 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 Applicant's Advisory Committee 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 30](#), 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

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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 30. Resected Tissue Volumes in CL0007

Parameter	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

Of 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. Pre-Surgery: Survey completed any time before the surgery
2. Initial post-surgical follow-up: Survey completed within 45 days after the surgery
3. 3 month: Survey completed between 45 and 135 days after the surgery
4. 6 month: Survey completed conducted more than 135 days after the surgery

[Table 31](#) 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.

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Table 31. 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 month	126 (35%)	58	68
6 month	50 (14%)	23	27

Source: Table 4-2 of Addendum to CL0007 Clinical Study Report.

Abbreviations: 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 32](#). 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 included the small number of respondents and the self-selection for participation in this portion of the study. However, they do not suggest that additional tissue resection driven by LUMISIGHT worsened cosmetic outcome.

Table 32. The Applicant Summary of Patient Satisfaction by the Groups With or Without Therapeutic Shaves

Time Frame	No Therapeutic Shave		At Least One Therapeutic Shave	
	N	Mean (95% CI)	N	Mean (95% CI)
Pre-Surgery	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 Month	58	73 (66.6, 79.4)	68	69.4 (64.1, 74.7)
6 Month	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

Dose/Dose Response

The nominal dose of LUMISIGHT for CL0007 was 1 mg/kg. The mean administered dose in the mITT population was 1 mg/kg, with range 0.94 to 1.05 mg/kg.

8.1.2. CL0006

8.1.2.1. Study Design

Overview and Objectives

Study CL0006 was a single-arm, multicenter clinical study undertaken to refine and verify the algorithm used by Lumicell DVS for detection of residual cancer tissue. Other objectives included training of breast cancer surgeons and hospital staff at the different sites and

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implementing a uniform method for orienting and inking the main specimen. This study had three phases. For this review, only the final Phase C portion is discussed.

Trial Design

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.

Study Endpoints

No hypothesis testing was specified in the study protocol. Post hoc analyses of efficacy endpoints similar to those of study CL0007 were performed. Refer to section [8.1.1](#).

Statistical Analysis Plan

The statistical analysis plan was developed after completion of CL0006. The study populations are defined identically as for CL0007. Refer to section [8.1.1](#).

Protocol Amendments

CL0006 protocol amendments are summarized in [Table 33](#).

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Table 33. Study CL0006 Protocol Amendments

Revision	Purpose	Release Date	Number and Percent of Patients Enrolled Under Protocol Version
A	Initial release	June 21, 2017	5 (2%)
B	Changes to eligibility criteria and other sections based on observed anaphylaxis	June 14, 2018	99 (42%)
03	Increase number of Lumicell guided shaves per orientation from 1 to 2	December 18, 2018	53 (23%)
04	Clarify the exclusion criterion for allergic reaction to polyethylene glycol	February 15, 2019	77 (33%)

Source: Table 9-4 of CL0006 Clinical Study Report.

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 based 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 will be included in the to be marketed product.

8.1.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the study was designed, conducted, and reported in compliance with GCPs.

Financial Disclosure

The Applicant certified that they have not entered into any financial arrangement with the study clinical investigators.

Patient Disposition

[Table 34](#) describes the disposition of patients. A total of 234 patients were injected with LUMISIGHT and included in the safety population. Four patients were withdrawn from the study after injection of LUMISIGHT but before completing the imaging procedure. This included one patient who had a hypersensitivity reaction, one patient who could not be imaged due to unavailability of personnel with expertise to operate the Lumicell DVS, and two patients who received blue dye prior to imaging. Thus, the mITT population contained 230 patients.

Table 34. Patient Disposition in CL0006

Disposition	Number (%) of Patients
Patients with informed consent form signed	283 (100%)
Screen failure	42 (15%)
Withdrawn prior to enrollment	7 (3%)

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Disposition	Number (%) of Patients
Patients with LUMISIGHT injected (Safety population)	234 (83%)
Patients withdrawn before completing Lumicell DVS imaging	4 (1%)
Patients who completed Lumicell DVS imaging (mITT population)	230 (81%)
Patients with major protocol deviations	5 (2%)
Patients in the per protocol population	225 (80%)

Source: Table 10-1 of CL0006 Clinical Study Report.

Abbreviations: DVS = direct visualization system, mITT = modified intent-to-treat

Protocol Violations/Deviations

There were 78 protocol deviations. A total of 53 protocol deviations occurring in 45 patients were classified as major. The most common major deviations were related to shave procedure not followed (n=22), image saving (n=13), and eligibility or screening assessment (n=10). Five patients were excluded from the efficacy analysis because of a protocol deviation: 3 patients received neoadjuvant letrozole and 2 patients had surgery start more than 6 hours after injection of LUMISIGHT. We note that the per protocol population was to exclude all major protocol deviations rather than selected major deviations. However, this does not affect the review as it does not rely on analyses performed in the per protocol population.

Table of Demographic Characteristics

Demographic characteristics of patients enrolled in CL0006 are presented in [Table 35](#). The distribution of age, sex, race, ethnicity, and body mass index are similar to those in CL0007.

Table 35. Table of Demographics

Characteristics	Safety Population (N = 234)	Modified Intent-to-Treat Population (N = 230)
Age (Years)		
Mean ± SD	61.7±9.8	61.4±9.7
Median (Range)	62 (37, 84)	62 (37, 84)
Race		
Asian	15 (6%)	15 (7%)
Black or African American	21 (9%)	21 (9%)
White	187 (80%)	183 (80%)
Multiple races	2 (<1%)	2 (<1%)
Unknown or Not reported	9 (4%)	9 (4%)
Ethnicity		
Hispanic or Latino	4 (2%)	4 (2%)
Non-Hispanic or Latino	220 (94%)	216 (94%)
Unknown or not reported	10 (4%)	10 (4%)
BMI (kg/m ²)		
Mean ± SD (N)	29.0±6.6	29.0±6.6
Median (Q1, Q3)	27.5 (17.1, 51.3)	27.4 (17.1, 51.3)

Source: Table 11-2 of CL0006 Clinical Study Report

Abbreviations: BMI = body mass index, Q = quartile, SD = standard deviation

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Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Tumor histology and genetic markers are presented in [Table 36](#). Approximately 70% of patients had IDC, which is consistent with the rate observed in CL0007. Tumor receptor status and preoperative lymph node status were also similar to CL0007.

Table 36. Tumor Histology, Receptor Status, and Preoperative Lymph Node Status in CL0006

Characteristics	mITT Population (N = 230)
Tumor histology	
DCIS only	43 (19%)
IDC +/- DCIS	160 (70%)
ILC +/- DCIS	25 (11%)
IDC + ILC	2 (<1%)
Receptor status	
ER (+)	209 (92%)
PR (+)	176 (80%)
HER2 (+)	18 (10%)
Triple negative	
Yes	10 (4%)
No	219 (95)
Unknown	1 (<1)
Preoperative lymph node status	
At least one LN (+)	28 (12%)
All LN (-)	156 (68%)
No LN biopsy	46 (20%)

Source: Table 11-4 of CL0006 Clinical Study Report

Note: Histology and receptor status information was derived from both pre-surgical and surgical pathology findings, with data from surgical specimen prioritized over pre-surgical biopsy if information captured in both sources.

Abbreviations: DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor-2; IDC = infiltrating ductal carcinoma; ILC = invasive lobular carcinoma; LN = lymph node; mITT = modified intent-to-treat; PR = progesterone receptor

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

LUMISIGHT was administered by study personnel and treatment compliance is not applicable.

Efficacy Results

The co-primary efficacy endpoints of CL0007 were applied to CL0006 retrospectively. As noted in Section [8.1.2.1](#), 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).

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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 (9%; 95% CI: 4%, 16%) for the validation set. In the extended training set, 17 of 127 patients (13%; 95% CI: 8%, 21%) had removal of residual cancer. The rate in the validation set is similar to that seen in CL0007 (8%; 95% CI: 5%, 11%). The significance of the trend to a higher rate in the extended training set is unknown. As shown in [Table 37](#), in the validation set the tissue-level sensitivity was 64% (95% CI: 41%, 81%) and specificity was 80% (95% CI: 76%, 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%, and the clinical consequence of this difference is doubtful.

Table 37. 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

Data Quality and Integrity

FDA OSI audits of the Applicant revealed no significant unresolved GCP deviations.

8.1.3. Integrated Assessment of Effectiveness

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

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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, we 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 underperformance of 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 a 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 all negative margins by LUMISIGHT are expected to have substantial benefit through avoidance of a second surgery. In CL0007, 9 patients (3% of the 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. The Applicant further 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. There is uncertainty regarding how many conversions to negative margins were attributable to accurate detection of cancer by LUMISIGHT.

In patients who do not convert from positive to negative margins, the benefit of removing additional cancer is unclear. 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](#)

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[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 such 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 low based on these results.

After considering the above issues, we find that the Applicant has submitted substantial evidence of effectiveness for LUMISIGHT as an adjunct to detect breast cancer within the resection cavity after completion of BCS. This evidence is composed of one adequate and well-controlled study (CL0007) and confirmatory evidence of effectiveness provided in CL0006.

8.2. Review of Safety

8.2.1. Safety Review Approach

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. In addition, after data lock for the Integrated Summary of Safety, 1 additional patient experienced an anaphylactic reaction and the Applicant incorporated this event into the NDA. Finally, a cardiovascular safety study enrolling healthy volunteers was included. All of these data sources were reviewed.

The Applicant excluded data from 10 patients enrolled in 2 additional studies of brain cancer and peritoneal metastasis, but states that none of these patients reported an AE (AE).

8.2.2. Review of the Safety Database

Overall Exposure

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. 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.

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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.

Relevant Characteristics of the Safety Population

As shown in [Table 38](#), the large majority of patients in the safety population are female, which is appropriate for a breast cancer imaging drug. The age of patients is similarly reasonable for purpose. Fewer patients of Black or African American race or of Hispanic or Latino ethnicity are present than expected based on the demographics of the United States population in general. However, we are not aware of evidence to suggest that race or ethnicity will affect likelihood or severity of AEs.

Table 38. Demographics of Safety Populations

Parameter	Overall Safety Population (N = 790)	1 mg/kg Oncology Population (N = 726)
Sex, n (%)		
Female	744 (94%)	711 (98%)
Age		
Mean (SD)	61 (11)	61.8 (9.9)
Median (range)	62 (19 – 86)	63 (36 – 86)
≥65 years, n (%)	348 (44%)	321 (44%)
≥75 years, n (%)	66 (8%)	61 (8%)
Race, n (%)		
American Indian or Alaska Native	1 (<1%)	1 (<1%)
Asian	44 (6%)	42 (6%)
Black or African American	67 (8%)	53 (7%)
Native Hawaiian or Pacific Islander	1 (<1%)	1 (<1%)
White	642 (81%)	597 (82%)
Other or Unknown	35 (4%)	32 (4%)
Ethnicity, n (%)		
Hispanic or Latino	21 (3%)	18 (3%)
Non-Hispanic or Latino	737 (93%)	677 (93%)
Unknown	32 (4%)	31 (4%)

Source: FDA clinical reviewer

Adequacy of the Safety Database

The size and demographic distribution of the safety database are acceptable for review.

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8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

Formal AE assessments were performed in all studies in the safety database. In most cases these assessments were performed on the day of LUMISIGHT administration and at the first postoperative visit. The first postoperative visit was scheduled per SoC with timing not limited by protocol. In study DUK1-12-137, AE severity was not documented. In all other studies, Common Terminology Criteria for Adverse Events version 4.03 or version 5 were used. AE relatedness was assessed using a 5-point scale for all studies except CLP0008, which used a 3-point scale. AEs assessed as related to surgery or routine post-operative medication were not included for DUK1-12-137. MedDRA coding of AEs was not specified in most studies. For the integrated summary of safety, the Applicant coded AEs using MedDRA version 22.1. Coding of verbatim terms was audited by the clinical team during the review and appeared reasonable.

The Applicant also collected adverse device effect data for Lumicell DVS in these studies. The Applicant reported no unanticipated adverse device effects or device issues that led to an AE (P230014 Executive Summary). Assessment of device safety is deferred to the CDRH review team.

Routine Clinical Tests

Post-LUMISIGHT administration vital sign data were obtained in a minority of patients, including patients in DUK1-12-137, CLP00201, and CL0005. In addition, the Applicant provided vital sign results for 6 patients who had received LUMISIGHT in clinical trials after data lock for the integrated summary of safety.

All studies in the safety database collected blood count and chemistry laboratory data at the final visit/routine follow up visit or for CLP0008, within 30 days of the routine follow up visit. Additional laboratory assessments were performed at earlier time points for studies DUK1-12-137 and CLP00201.

Urinalysis data were not found in the safety database.

ECG data were collected after LUMISIGHT administration only in studies DUK1-12-137 and CLP00201.

8.2.4. Safety Results

Deaths

No deaths were reported.

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Serious Adverse Events

A total of 11 SAEs were recorded in 9 patients in the Overall Safety population. Of these, 4 SAEs in 4 patients were categorized by the investigator as related to LUMISIGHT. These events were anaphylactic reaction (n=3) and hypersensitivity (n=1), and are discussed in detail as a submission-specific safety issue in section 8.2.5. The remaining 7 SAEs in 5 patients included intestinal pseudo-obstruction, deep vein thrombosis, somnolence and acute respiratory failure in the same patient, acute kidney injury and breast cellulitis in the same patient, and vascular pseudoaneurysm. Intestinal pseudo-obstruction and deep vein thrombosis occurred in patients with cancers other than breast cancer who were dosed at 0.5 mg/kg. All other SAEs occurred in patients with breast cancer who were intended to receive 1 mg/kg LUMISIGHT.

- Intestinal pseudo-obstruction: This event occurred 9 days after drug administration. Given this timing and because postoperative state is a risk factor for intestinal pseudo-obstruction, we agree with categorization of this event as non-drug-related.
- Deep vein thrombosis: This event occurred 14 days after drug administration. Given this timing and because postoperative state is a risk factor for deep vein thrombosis, we agree with categorization of this event as non-drug-related.
- Somnolence and acute respiratory failure: A 69-year-old female with breast cancer who had a history of polio and post-polio syndrome with vocal cord dysfunction, history of difficult intubation, and sleep apnea experienced these events approximately 7 hours after LUMISIGHT administration. She had an uneventful BCS, but on transfer to the post-anesthesia care unit was found to be unresponsive with minimal respiratory effort. After intubation, she became hypotensive and was transferred to the emergency department, and eventually the intensive care unit. Workup included chest CT negative for pulmonary embolus, echocardiogram with normal ejection fraction, cardiac catheterization with minimal coronary artery disease, and airway endoscopy with vocal cord paralysis. These events were assessed as unrelated to LUMISIGHT by the investigator. No competing etiology was proposed in the narrative summary. While an effect of anesthesia drugs seems more likely, relatedness to LUMISIGHT cannot be excluded.
- Acute kidney injury and breast cellulitis: Acute kidney injury was diagnosed in this 70-year-old female with history of chronic kidney disease, coronary atherosclerosis, diastolic heart failure, hypertension, and hyperlipidemia 17 days after administration of LUMISIGHT at a routine postoperative assessment. Creatinine had increased from 1.47 mg/dL (eGFR 42 mL/min/1.73 m²) preoperatively to 2.28 mg/dL (eGFR 25 mL/min/1.73 m²). Blood urea nitrogen was also increased at 35 mg/dL, and the investigator assessed the patient as being dehydrated. Breast cellulitis near the surgical incision was also diagnosed at the follow up visit on day 17. Based on timing and presence of more likely etiologies, we agree with categorization of these events as non-drug-related.
- Vascular pseudoaneurysm: A 53-year-old female with history of chest pain and left heart catheterization 9 days prior to LUMISIGHT administration reported an enlarging right

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groin mass at the time of her lumpectomy. The next day, she reported pain associated with the mass and had surgical repair of the pseudoaneurysm. Based on presence of a more likely etiology, we agree with categorization of this event as non-drug-related.

Examination of the safety database revealed 2 AEs in 2 patients that resulted in hospitalization but were not categorized by the Applicant as SAEs. These events included hypotension in the same patient who had somnolence and acute respiratory failure, discussed above, and pneumonia occurring 18 days after administration of 1.5 mg/kg LUMISIGHT.

Dropouts and/or Discontinuations Due to Adverse Effects

Eight patients experienced 9 AEs leading to study discontinuation. The events leading to discontinuation were hypersensitivity (n=3), anaphylactic reaction (n=2), extravasation (n=2), skin discoloration (n=1, coexisting with extravasation), and nausea (n=1). All of these events were considered related to LUMISIGHT. Note that the anaphylactic reactions and one of the cases of hypersensitivity were classified as SAEs.

Significant Adverse Events

In total, 16 severe AEs were reported in 13 patients (1.6%) in the Overall Safety population ([Table 39](#)). Five of the severe AEs were considered related to LUMISIGHT by the investigator. The intended dose was 1 mg/kg for 14 severe AEs, and 13 of the severe AEs occurred in patients with breast cancer. Seven severe AEs were also classified as serious and are discussed above. Note that the events of hypotension and acute myocardial infarction occurred in the same patient as the SAEs of somnolence and acute respiratory failure.

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Table 39. Listing of Patients With Severe Adverse Events in the Overall Safety Population

Race/Sex/Age	Dose (mg/kg)	Preferred Term	Start Date/ End Date	Severity	SAE	Relatedness	Action	Outcome
White/M/65	0.5	Intestinal pseudo-obstruction	(b) (6)	Severe	Yes	Unrelated	Hospitalization/ prolonged hospitalization	Resolved
White/M/61	1	Presyncope		Severe	No	Unrelated	Medication required	Resolved
White/F/77	1.5	Pneumonia		Severe	No	Unrelated	Hospitalization/ prolonged hospitalization	Resolved
White/F/53	1	Alanine aminotransferase increased		Severe	No	Related	No action needed	Resolved
White/F/69	1	Acute myocardial infarction		Severe	No	Unrelated	Non-drug treatment	Resolved
	1	Hypotension		Severe	No	Unrelated	Medication/ non-drug treatment/ hospitalization	Resolved
White/F/47	1	Hypersensitivity		Severe	Yes	Related	Medication/ withdrawal from study	Resolved
Asian/F/46	1	Breast pain		Severe	No	Unrelated	Medication	Resolved with sequelae
White/F/70	1	Breast cellulitis		Severe	Yes	Unrelated	Medication/ hospitalization	Resolved
	1	Acute kidney injury		Severe	Yes	Unrelated	Non-drug treatment/ hospitalization/other	Resolved
	1	Chronic kidney disease		Severe	No	Unrelated	Non-drug treatment/ other	Not resolved

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Race/Sex/Age	Dose (mg/kg)	Preferred Term	Start Date/ End Date	Severity	SAE	Relatedness	Action	Outcome
White/F/53	1	Vascular pseudoaneurysm	(b) (6)	Severe	Yes	Unrelated	Hospitalization	Resolved
White/F/80	1	Back pain		Severe	No	Unrelated	Other	Resolved
White/F/49	1	Hypersensitivity		Severe	No	Related	Medication/ withdrawal from study	Resolved
White/F/40	1	Anaphylactic reaction		Severe	Yes	Related	Medication/ withdrawal from study	Resolved
White/F/61	1	Anaphylactic reaction		Severe	Yes	Related	Medication	Resolved

Source: Table 8 in ISS and FDA reviewer.

Abbreviations: ISS = integrated summary of safety, F = female; M = male; SAE = serious adverse event.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 1005 AEs were reported in 678 patients in the Overall Safety population, and 926 AEs in 633 patients in the 1 mg/kg Oncology population. Adverse events are summarized by MedDRA system organ class in [Table 40](#). The most common class of AEs was renal and urinary disorders, accounting for 67% of all AEs in the 1 mg/kg Oncology population. Most (89%) AEs in this population were mild in intensity, with 70 (8%) being moderate, 14 (2%) severe, 3 (<1%) life threatening, and 13 (1%) lacking severity information.

Table 40. Treatment Emergent Adverse Events by System Organ Class

MedDRA System Organ Class	Overall Safety Population (n = 790)		1 mg/kg Oncology Population (n = 726)	
	N AEs	n (%) Patients	n AEs	n (%) Patients
At least one AE	1005	678 (86%)	926	633 (87%)
Renal and urinary disorders	662	657 (83%)	619	614 (85%)
Injury, poisoning and procedural complications	66	57 (7%)	66	57 (8%)
General disorders and administration site conditions	43	34 (4%)	33	26 (4%)
Skin and subcutaneous tissue disorders	43	36 (5%)	40	33 (5%)
Gastrointestinal disorders	38	31 (4%)	29	25 (3%)
Reproductive system and breast disorders	32	26 (3%)	32	26 (4%)
Nervous system disorders	18	15 (2%)	15	14 (2%)
Infections and infestations	15	14 (2%)	11	10 (1%)
Musculoskeletal and connective tissue disorders	15	12 (2%)	13	10 (1%)
Investigations	14	10 (1%)	14	10 (1%)
Respiratory, thoracic, and mediastinal disorders	13	8 (1%)	12	7 (<1%)
Vascular disorders	13	12 (2%)	11	10 (1%)
Immune system disorders	8	8 (1%)	8	8 (1%)
Metabolism and nutrition disorders	8	6 (<1%)	7	5 (<1%)
Psychiatric disorders	6	5 (<1%)	5	4 (<1%)
Cardiac disorders	4	2 (<1%)	4	2 (<1%)
Blood and lymphatic system disorders	2	2 (<1%)	2	2 (<1%)
Ear and labyrinth disorders	2	2 (<1%)	2	2 (<1%)
Eye disorders	2	2 (<1%)	2	2 (<1%)
Surgical and medical procedures	1	1 (<1%)	1	1 (<1%)

Source: FDA clinical reviewer

Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities

Chromaturia was the most frequently reported AE, with 614 of 726 patients (85%) in the 1 mg/kg Oncology population experiencing it ([Table 41](#)). Excluding chromaturia from analysis, 176 of 726 (24%) patients had at least 1 AE. Several of the most commonly reported non-chromaturia AEs, such as seroma, breast pain, and procedural pain, appear to be known risks of BCS.

Table 41. Adverse Events Occurring in at Least 3 Patients in the Overall Safety Population

MedDRA Preferred Term	Overall Safety Population (N=790)		1 mg/kg Oncology Population (N=726)	
	n Patients	%	n Patients	%
Chromaturia	657	83%	614	85%
Seroma	31	4%	31	4%
Breast pain	22	3%	22	3%
Nausea	20	3%	17	3%
Fatigue	15	2%	11	2%
Pain	12	2%	7	<1%
Procedural pain	11	1%	11	2%
Rash	9	1%	6	<1%
Contusion	8	1%	8	1%
Pruritus	8	1%	8	1%
Constipation	6	<1%	5	<1%
Ecchymosis	6	<1%	6	<1%
Erythema	6	<1%	6	<1%
Hematoma	6	<1%	6	<1%
Extravasation	4	<1%	4	<1%
Alanine aminotransferase increased	4	<1%	4	<1%
Blood creatinine decreased	4	<1%	4	<1%
Hypersensitivity	4	<1%	4	<1%
Hypoesthesia	4	<1%	4	<1%
Rash maculo-papular	4	<1%	4	<1%
Vomiting	4	<1%	4	<1%
Back pain	3	<1%	2	<1%
Cough	3	<1%	3	<1%
Decreased appetite	3	<1%	2	<1%
Oropharyngeal pain	3	<1%	3	<1%
Postoperative wound infection	3	<1%	1	<1%
Pyrexia	3	<1%	2	<1%
Anaphylactic reaction	3	<1%	3	<1%
Headache	3	<1%	2	<1%
Pain in extremity	3	<1%	2	<1%

Source: FDA clinical reviewer

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

The investigator-assessed adverse reactions (ARs) from LUMISIGHT are summarized in [Table 42](#). Chromaturia was the most frequently reported AR, occurring in 83% to 85% of pooled safety populations. Other than chromaturia, no ARs were reported at the 0.5 and 1.5 mg/kg treatment levels.

In the primary safety analysis population, 29 patients had a related AE other than chromaturia ([Table 42](#)). The most frequent ARs were hypersensitivity, and blood creatinine decreased, occurring in 4 patients each, as well as anaphylactic reaction and extravasation, occurring in 3 patients each. Several of the events assessed as related, including breast cellulitis, urinary tract infection, and post-traumatic stress disorder, seem unlikely to be caused by the drug. Extravasation and contusion are more likely related to the administration of LUMISIGHT than the drug itself, and are general risks of intravenous drug administration. The clinical significance of decreased blood creatinine in this context is doubtful.

Table 42. Adverse Events Other Than Chromaturia Assessed as Related by Study Investigators

Category	Overall Safety Population (N = 790)		1.0 mg/kg Oncology Population (N = 725)	
	n Patients	%	n Patients	%
AEs other than chromaturia	31	4%	29	4%
Gastrointestinal disorders	4	<1%	3	<1%
Abdominal pain	1	<1%	0	0
Nausea	2	<1%	2	<1%
Vomiting	1	<1%	1	<1%
General disorders and administration site conditions	4	<1%	4	<1%
Extravasation	3	<1%	3	<1%
Pyrexia	1	<1%	1	<1%
Immune system disorders	7	<1%	7	<1%
Anaphylactic reaction	3	<1%	3	<1%
Hypersensitivity	4	<1%	4	<1%
Infections and infestations	2	<1%	2	<1%
Breast cellulitis	1	<1%	1	<1%
Urinary tract infection	1	<1%	1	<1%
Injury, poisoning and procedural complications	3	<1%	3	<1%
Contusion	1	<1%	1	<1%
Procedural pain	2	<1%	2	<1%
Investigations	8	1%	8	1%
Alanine aminotransferase increased	2	<1%	2	<1%
Aspartate aminotransferase increase	1	<1%	1	<1%
Blood creatinine decreased	4	<1%	4	<1%
Glomerular filtration rate decreased	1	<1%	1	<1%
Musculoskeletal and connective tissue disorders	1	<1%	0	0
Pain in extremity	1	<1%	0	0
Nervous system disorders	2	<1%	1	<1%
Dysgeusia	1	<1%	1	<1%
Head discomfort	1	<1%	0	0
Psychiatric disorders	1	<1%	1	<1%
Post-traumatic stress disorder	1	<1%	1	<1%
Respiratory, thoracic, and mediastinal disorders	2	<1%	1	<1%
Dyspnea	1	<1%	1	<1%
Oropharyngeal discomfort	1	<1%	0	0
Skin and subcutaneous tissue disorders	5	<1%	5	<1%
Pruritus	1	<1%	1	<1%
Rash maculo-papular	2	<1%	2	<1%
Skin discoloration	1	<1%	1	<1%
Urticaria	1	<1%	1	<1%
Vascular disorders	2	<1%	1	<1%
Hot flush	1	<1%	0	0
Thrombophlebitis superficial	1	<1%	1	<1%

Source: FDA clinical reviewer

Note: A related AE is an AE with a relationship of probably or definitely.

Abbreviations: AE = adverse event

Laboratory Findings

A blood draw was collected for a complete blood count and serum chemistry tests at the first postoperative visit. As noted in the adverse event analysis, changes in aspartate aminotransferase and alanine aminotransferase were recorded as AEs. A shift analysis ([Table 43](#)) showed that more patients had normal aminotransferase, alkaline phosphatase, or bilirubin levels at baseline increasing to abnormal after treatment than changed in the other direction. However, only a few of patients had levels more than twice the upper limit of normal. No Hy's Law case was identified. Attribution of this result to LUMISIGHT is difficult due to the potential for confounding by surgery and anesthesia.

Table 43. Summary of Liver Related Lab Tests

Lab Measurement	Normal at Baseline and High After Treatment, n (%)	High at Baseline and Normal After Treatment, n (%)	Patients With > 2x ULN (n)
Alkaline phosphatase	16 (2.5%)	5 (0.8%)	1
Alanine aminotransferase	22 (3.5%)	15 (2.4%)	3
Aspartate aminotransferase	18 (2.8%)	9 (1.4%)	2
Bilirubin	6 (1%)	3 (0.5%)	2

Source: FDA clinical reviewer

Abbreviations: ULN = upper limit of normal

Changes in creatinine were also recorded as AEs. No clear trend of eGFR changes after administration of LUMISIGHT was identified.

Vital Signs

Vital signs were collected as a screening parameter, but were not systematically recorded as study data after injection of LUMISIGHT.

Electrocardiograms

No ECG monitoring was reported.

QT

A thorough QT study was not performed. The CLP002021 cardiovascular safety study was evaluated by the QT Interdisciplinary Review Team and found to be acceptable as a substitute

for a thorough QT study. Data did not suggest that pegulicanine is associated with increases in the QT interval.

8.2.5. Analysis of Submission-Specific Safety Issues

Anaphylaxis and Serious Hypersensitivity

Due to the incidence of anaphylactic reaction and other serious hypersensitivity adverse events, FDA Division of Pulmonology, Allergy, and Critical Care consultation was obtained. The Division's input is summarized in this section.

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.

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 44](#). 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 44. 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 45](#). 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 45. 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

*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 [16.4](#)) 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 46](#) and provided in more detail in section [16.5](#).

Table 46. 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 46](#) 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 47](#) summarizes the limited available information for AEs identified using the Hypersensitivity (Broad) FMQ and deemed related to IP by the investigator, as listed in [Table 45](#) but excluding the four reactions adjudicated as anaphylaxis. More detailed narratives are provided in section [16.5](#).

Table 47. 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

Patient Identifier (Age, years)	Onset	Severity*	AE PT	Relevant Signs, Symptoms, and Laboratory Results	Action Taken	Outcome
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)
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 3	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 6 patients in [Table 47](#) had events that resolved in 24 hours or less, while 3 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, 3 at an unspecified time afterwards, and 1 at an unspecified time that may have been before or after IP. Tryptase and total complement levels were assessed in none of these 6 patients, and histamine was assessed in only 1, and was elevated. Based on the limited provided information, up to 2 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](#)).

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](#)).

A potential approach for management of this risk would be to slow the rate of LUMISIGHT infusion. 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](#)).

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Safety COA data were not collected and were not needed.

8.2.7. Safety Analyses by Demographic Subgroups

The number of males in the safety population is insufficient for an analysis of AE incidence by sex. There was a trend to more AEs assessed as related in patients younger than 65 ([Table 48](#)), however this analysis is limited by the small number of patients with AEs assessed as related. Only two subgroups were considered for analysis by race due to the enrollment of predominantly white patients, but no difference in incidence of AEs was seen ([Table 49](#)).

Table 48. Patients with At Least 1 Adverse Event Other Than Chromaturia by Age in the 1 mg/kg Oncology Population (N=726)

Parameter	Age <65	Age ≥65
Patients, n (%)	405 (56%)	321 (44%)
Patients with any non-chromaturia AE, n (%)	105 (60%)	71 (40%)
Patients with any related non-chromaturia AE, n (%)	21 (72%)	8 (28%)

Source: FDA clinical reviewer

Table 49. Patients with At Least 1 Adverse Event Other Than Chromaturia by Race in the 1 mg/kg Oncology Population (N=726)

Parameter	White	Not White
Patients, n (%)	597 (82%)	129 (18%)
Patients with any non-chromaturia AE, n (%)	147 (84%)	29 (16%)
Patients with any related non-chromaturia AE, n (%)	25 (86%)	4 (14%)

Source: FDA clinical reviewer

8.2.8. Specific Safety Studies/Clinical Trials

Complement Activation Sub-Study

After observing the first case of anaphylactic reaction in the development program, in study CL0006, the Applicant conducted a sub-study to evaluate the potential of LUMISIGHT to induce a Type I hypersensitivity response. A total of 18 patients enrolled in CL0006 had evaluation of changes in levels of three laboratory measures, serum histamine, tryptase, and complement, prior to and 10, 30, and 60 minutes after administration of 1 mg/kg LUMISIGHT. On average, no statistically significant changes from baseline were reported in any of the laboratory values at any of the time points. As this study was conducted in patients who were not having an acute reaction, the results are primarily useful as a reference for similar laboratory analyses in patients who later experienced a hypersensitivity reaction.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies of carcinogenicity were performed, and none were needed.

Human Reproduction and Pregnancy

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

Pediatrics and Assessment of Effects on Growth

LUMISIGHT is not intended for use in children.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The largest dose investigated in the LUMISIGHT development program was 4 mg/kg, or 4-fold the to be marketed dose. No potential for drug abuse is expected.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. At the time of NDA submission, LUMISIGHT has not been marketed in any country.

Expectations on Safety in the Postmarket Setting

To better understand the risk, the FDA will require a postmarketing safety study that measures rates of anaphylaxis and other hypersensitivity reactions and characterizes the reactions. Such a study may provide incidence estimates in clinical practice 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. This study will also augment the limited amount of currently available vital sign safety data.

Enhanced pharmacovigilance for hypersensitivity reactions, including anaphylaxis, will also be employed. Enhanced pharmacovigilance will 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.

8.2.11. Integrated Assessment of Safety

The major safety concern for LUMISIGHT is anaphylaxis and other serious hypersensitivity reactions. 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. To increase awareness of the risk, a boxed warning has been added to the PI.

8.3. Statistical Evaluation

This 505(b)(1) NDA submission contains data from the pivotal clinical study (Study CL0007) and the clinical feasibility study (Study CL0006) of LUMISIGHT, an investigational new molecular entity optical imaging drug to detect cancerous tissue remaining in the lumpectomy cavity after excising the primary specimen during BCS. The Applicant also submitted a premarket application to CDRH for the Lumicell DVS, an investigational imaging device displaying suspected abnormal tissues that emit LUMISIGHT signal above a normal tissue fluorescence threshold. LUMISIGHT and Lumicell DVS together comprise the LUM Imaging System.

8.3.1. Study CL0007

In Study CL0007, a total of 406 patients scheduled for lumpectomy for histologically confirmed primary invasive breast cancer with or without DCIS or DCIS only were enrolled at 14 sites in the US, injected with LUMISIGHT, and proceeded to a SoC lumpectomy that could include selective or comprehensive shaves.

Eligible patients were randomized in a 10:1 ratio to either the investigational arm (referred to as the device arm in Section [8.1.1](#)) or the control arm to reduce the potential for a surgeon's under-calling bias during SoC surgery. Surgeons were unaware of the randomization status for a specific patient until the SoC lumpectomy surgical procedure was completed.

If a patient was in the investigational arm, after completion of SoC surgery, the surgeon proceeded to scan the surgical cavity wall using the Lumicell DVS, recorded the fluorescence status of each orientation of the cavity (superior, inferior, posterior, anterior, lateral, and medial), and removed fluorescence-guided shaves (therapeutic shaves) where indicated. For the control arm, the surgical cavity was not imaged with the Lumicell DVS after the SoC procedure. All resected tissues from SoC lumpectomy procedure and therapeutic Lumicell-guided shaves were sent to pathology for tumor assessment.

Out of 406 enrolled patients, 14 were withdrawn from the study after injection of LUMISIGHT but prior to randomization. Therefore, a total of 392 patients were randomized to either the investigational arm (n = 357) or the control arm (n = 35). Efficacy was evaluated in the 357 patients randomized to the investigational arm only, which is the Applicant’s defined mITT population.

- Co-primary efficacy endpoint 1: the proportion of patients having residual cancer found in at least 1 Lumicell-guided therapeutic shave among all patients in the investigational arm.

Residual cancer is defined as tumor found by pathology in a therapeutic shave after the SoC surgical procedure is completed, that is, tumor that SoC surgery failed to remove. The proportion was evaluated for H_0 : proportion $p \leq 3\%$ versus H_1 : proportion $p > 3\%$ using an exact binomial test at a 1-sided significance level of 2.5% on the mITT population. Successful evaluation results (the lower bound of the 95% confidence interval of the proportion exceeding the performance goal of 3%) for co-primary efficacy endpoint 1 based on either the mITT population or the ITT population are shown in [Table 50](#).

Table 50. Co-primary Efficacy Endpoint 1 Analysis Results in the mITT and ITT Populations

Co-primary Efficacy Endpoint 1	Performance Goal	Estimated Proportion (95% CI)
Proportion of patients having residual cancer found in at least 1 therapeutic shave in the mITT population	> 3%	27 / 357 = 7.6% (5.0%, 10.8%)
Proportion of patients having residual cancer found in at least 1 therapeutic shave in the ITT* population	> 3%	27 / 371 = 7.3% (4.9%, 10.4%)

Source: Table 21 of CL0007 Clinical Study Report
* The ITT population included 14 withdrawn patients who received LUMISIGHT.
Abbreviations: CI = confidence interval, ITT = intent-to-treat, mITT = modified intent-to-treat

Of the 27 patients with at least 1 therapeutic shave containing cancer, 8 had positive SoC surgical margins and 19 had negative SoC surgical margins.

- Co-primary efficacy endpoints 2 and 3: tissue-level sensitivity and specificity of fluorescence status in the lumpectomy cavity following SoC surgery.

Sensitivity, defined as $TPs / (TPs + FNs)$, and specificity, defined as $TNs / (TNs + FPs)$, at the tissue-level were evaluated using the definition shown in [Table 51](#). For the tissue-level endpoints, each orientation 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 the analyses of these endpoints. If there

was sufficient tissue to allow a shave, the number of observations included in the tissue-level endpoints for the orientation was generally equal to the number of therapeutic shaves plus 1.

Table 51. Definition of Elements Used to Calculate Tissue-Level Sensitivity and Specificity

LUMISIGHT Signal	Standard of Truth	
	Positive	Negative
Positive	True positive (TP)	False positive (FP)
Negative	False negative (FN)	True negative (TN)

Source: Table 1 of statistical analysis plan for CL0007

The standard of truth (SoT) used for comparison to the fluorescence status of each tissue was determined using a hierarchical approach ([Figure 16](#)). The description below is at high level. Details on the handling of multiple images in an orientation can be found in [Section 8.1.1](#).

1. The highest SoT is whether histopathology identifies cancer in a therapeutic shave that was removed.
2. If a therapeutic shave does not exist, then whether tumor is found from the first-time re-excision from a follow-up surgery at the orientation is considered the SoT.
3. If neither a therapeutic shave nor a second surgery exists for the tissue, the margin assessment of the last resected specimen from the orientation is used as the SoT (inferred SoT).

Tissue-level sensitivity and specificity were evaluated for H_0 : sensitivity $\leq 40\%$ versus H_1 : sensitivity $> 40\%$, and for H_0 : specificity $\leq 60\%$ versus H_1 : specificity $> 60\%$ using a generalized estimating equation (GEE) to account for correlation of tissues from the same patient at a 2-sided 5% significance level. Results of co-primary efficacy endpoints 2 and 3 are shown in [Table 52](#). Tissue-level specificity exceeded the performance goal of 60% and tissue-level sensitivity did not meet the performance goal of 40%. The FDA statistics review team performed an exploratory analysis assuming tissues within a patient are independent. The results between GEE and FDA exploratory analyses are similar, suggesting that the correlation among tissues within patients appears low.

Table 52. Co-primary Efficacy Endpoints 2 and 3 Analysis Results in the mITT Population

Primary Efficacy Endpoint	Performance Goal	Proportion Estimate (95% CI)
Tissue-level sensitivity (GEE)	> 40%	49.1% (36.4%, 61.9%)
Tissue-level sensitivity (unadjusted)*		49.3% (38.0%, 61.6%)
Tissue-level specificity (GEE)	> 60%	86.5% (84.5%, 88.3%)
Tissue-level specificity (unadjusted)*		85.2% (83.4%, 86.6%)

Source: Table 21 of CL0007 Clinical Study Report and FDA statistical reviewer

* FDA unadjusted analyses assume independence among tissues in a patient.

Abbreviations: CI = confidence interval, GEE = generalized estimating equation, mITT = modified intent-to-treat

[Table 53](#) shows the distribution of tissues of the mITT population by their fluorescence and cancer status.

Table 53. Contingency Table for Tissue-Level Sensitivity and Specificity in the mITT Population

		Standard of Truth		
		Positive	Negative	Total
LUMISIGHT signal	Positive	34	337	371
	Negative	35	1940	1975
	Total	69	2277	2346

Source: Table 25 of CL0007 Clinical Study Report

Abbreviations: mITT = modified intent-to-treat

- Clinically important secondary efficacy endpoint: the conversion rate of SoC positive margins to negative margins by removing therapeutic shaves.

The disposition of patients with SoC positive margins was as follows:

- o 62 patients had positive margins after SoC surgery,
- o LUMISIGHT was positive for at least 1 positive-margin orientation in 15 of 62 patients,
- o LUMISIGHT was positive for all positive-margin orientations in 10 of 15 patients,
- o 9 out of the 10 patients attained negative margins by removing therapeutic shaves

Therefore, the conversion rate of positive margin to negative margin due to removal of therapeutic shaves among patients who had positive SoC margin is $9 / 62 = 14.5\%$ (95% CI: 6.9%, 25.8%). It is noted that 8 of these 9 patients had no cancer identified in their therapeutic shaves.

Review Issue 1

Tissue-level sensitivity, 1 of the 3 co-primary efficacy endpoints, did not meet the pre-specified performance goal of 40%. Still, LUMISIGHT may provide diagnostic utility in detecting residual cancer.

Based on the tissue-level data presented in [Table 53](#), FDA statistics team performed an exploratory analysis to estimate tissue-level accuracy. Note that tissue-level accuracy, a measure of the proportion of tissues correctly identified by LUMISIGHT, is a summary measure and was not a pre-specified endpoint. The estimated tissue-level accuracy was 84.1% (95% CI: 82.6%, 85.6%), suggesting LUMISIGHT's diagnostic performance appears to be better than random chance of 50:50.

Review Issue 2

Out of 9 patients who converted from SoC positive margins to negative margins by removing therapeutic shaves, only 1 patient had cancer found in the therapeutic shave. The Applicant's explanation for false positive therapeutic shaves resulting in conversion from positive to negative margins is that LUMISIGHT is activated not only by tumor itself but also by the invasive front beyond tumor boundaries. To investigate the Applicant's hypothesis, positive fluorescence rates are compared among 3 distinct groups of tissues as an exploratory analysis and summarized in [Table 54](#). The analysis included only tissues directly facing SoC specimen margins, i.e., excluding tissues exposed after therapeutic shaves.

Group 1: Tissues corresponding to where margins of SoC lumpectomy specimens are negative.

- Group 2: Tissues corresponding to where margins of SoC lumpectomy specimens contain tumor within 2 mm from ink but not on ink of SoC lumpectomy specimens.
- Group 3: Tissues corresponding to where tumor is present on ink of SoC lumpectomy specimens.

Table 54. Positive Fluorescence Rates along with 95% Confidence Interval in Groups 1, 2, and 3

Group	Positive Fluorescence Rate (95% CI)
Group 1	226 / 2048 = 11.0% (9.8%, 12.5%)
Group 2	6 / 45 = 13.3% (6.3%, 26.2%)
Group 3	12 / 56 = 21.4% (12.7%, 33.8%)

Source: FDA statistical reviewer
Abbreviations: CI = confidence interval

From post-hoc defined tissue subgroups, the distribution of the observed tissues in the investigational arm yielded 2048 issues in group 1, 45 tissues in group 2, and 56 tissues in group 3. From [Table 54](#), the observed data suggest an increasing trend of positive fluorescence rate in the surgical cavity with decreasing distance between tumor and SoC specimen ink. Note that this analysis reports observations from the investigational arm only. No statistical inference can be made. Although there seems to be a trend, this exploratory analysis is limited in preliminarily supporting the Applicant’s hypothesis.

8.3.2. Study CL0006

Study CL0006, also called Feasibility Phase C Study, was an open-label, single-arm (non-randomized), multi-center clinical study undertaken to refine and validate the algorithm used by the imaging device for detection of residual cancer. This was an exploratory study performed in up to 5 patients per surgeon, with 1 to 3 surgeons per site and 16 sites in United States. The statistical analyses in this study were all retrospective, and there was no prespecified statistical analysis plan. The study had 230 patients in mITT population divided into two subpopulations of 127 patients in an extended training set and 103 patients in a validation set depending on the tumor detection algorithm used with the Lumicell DVS (original or refined). The analysis results of this study were not verified by the FDA statistical team. Refer to section [8.1.2.2](#) for an overview of the results.

The statistical review team acknowledges that this study is a feasibility study designed to validate the refined algorithm developed using the training dataset. The statistics provided are for estimation purposes. There was no pre-specified hypothesis to be tested nor was there a control arm to minimize the potential for bias of surgeons during performance of the SoC BCS procedure. While study CL0006 was not considered adequate and well-controlled, it was considered appropriate for confirmatory evidence of effectiveness.

8.4. Conclusions and Recommendations

Results of one adequate and well-controlled study (CL0007) and one study that provided confirmatory evidence of effectiveness (CL0006) demonstrate adequate diagnostic performance of LUMISIGHT for detection of breast cancer in the resection cavity after standard of care breast conserving surgery. The major safety issue for LUMISIGHT is anaphylaxis and

other serious hypersensitivity reactions. At a meeting of the Medical Imaging Drugs Advisory Committee, many Committee members commented that the benefit was modest but that the risks were manageable with appropriate labeling and post-marketing evaluation. We concur with this position and find that the benefit-risk balance for LUMISIGHT is favorable overall. Approval of this application is recommended.

9. Advisory Committee Meeting and Other External Consultations

A meeting of the Medical Imaging Drugs Advisory Committee was held on March 5, 2024, to discuss the persuasiveness of the evidence of performance of LUMISIGHT and to obtain advice on risk mitigation for hypersensitivity reactions, including anaphylaxis, to inform the benefit-risk assessment for LUMISIGHT. A summary of the discussion of the issues requested for committee input follows.

1. Discuss whether the observed performance of pegulicianine for patient-level detection of residual cancer, tissue-level sensitivity, and tissue-level specificity provide sufficient evidence of effectiveness.

Committee Discussion: *The Committee members were in general agreement that there was a modest overall benefit observed with use of pegulicianine, as it met its prespecified endpoints for patient-level detection of residual cancer and tissue-level specificity, but did not meet its tissue-level sensitivity goal. Some members pointed out that even small improvements can be valuable to patients with cancer, and acknowledged that while pegulicianine shows promise, it was not considered a “home run” or a “magical” solution, but rather an incremental benefit that is an important step forward in breast cancer management. Other members agreed there is a potential to observe better performance of pegulicianine with increased use and improved proficiency and technique among surgeons. One member stressed the need to consider the impact on individual patients and their families when evaluating the effectiveness of medical interventions. Another member expressed concern with setting a precedent for use of tissue-level metrics to support effectiveness. Other members raised concerns regarding the significance of the observed benefits, with emphasis on the relatively small number of patients who avoided a second surgery, a secondary analysis that was not the focus of the trial.*

2. Discuss the risk of serious hypersensitivity reactions associated with pegulicianine and the adequacy of risk mitigation and assessment strategies under consideration.

Committee Discussion: *In discussing the risk of serious hypersensitivity reactions associated with pegulicianine and the adequacy of risk mitigation and assessment strategies under consideration, Committee members were in overall agreement that adverse reactions are a concern. However, the majority of participants voiced that given the pre-surgical setting in which the patients would be administered the drug, the risk of hypersensitivity reactions is manageable and does not outweigh incremental benefits associated with pegulicianine. One member raised concerns about the number of serious adverse reactions observed in the trial*

relative to the number of patients benefiting from the treatment, and there was general agreement that additional safety data collection through a post-marketing study would be valuable to better understand the incidence of adverse reactions. Most committee members did not support the implementation of a Risk Evaluation and Mitigation Strategy (REMS), considering it unnecessary for this particular drug. Suggestions for risk mitigation included labeling recommendations for monitoring of patients during infusion and immediate access to medical care in case of adverse reactions. The possibility of pretreatment with antihistamines was discussed, with one member suggesting it could be considered based on individual patient factors and clinical judgment.

3. **VOTE:** Do the benefits of pegulicianine outweigh its risks?

- 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 pegulicianine.

Vote Result: Yes: 16 No: 2 Abstain: 1

Committee Discussion: The majority of Committee members voted "Yes" on whether the benefits of pegulicianine outweigh its risks. Many members cited the incremental benefits of pegulicianine in detection of residual cancer, as well as the manageable nature of the associated risks, such as hypersensitivity reactions. Suggestions for risk mitigation and assessment included labeling recommendations for monitoring, a post-marketing safety study, and enhanced pharmacovigilance. Some participants expressed concerns about the small absolute benefit and recommended clear patient-level information to set realistic expectations for patients who choose to undergo lumpectomy using pegulicianine.

Two Committee members voted "No," with one member acknowledging that while pegulicianine appears to detect residual cancer, the clinical utility of pegulicianine is still questionable without clear evidence of improved patient outcomes. Both Committee members, in addition to the one abstention, advocated for randomized trials to assess the effectiveness of pegulicianine in reducing reoperations.

10. Pediatrics

Incidence of breast cancer is extremely low in the pediatric population making it infeasible to conduct pediatric studies for the proposed indication. On October 17, 2023, the FDA Pediatric Review Committee agreed to grant a full waiver of pediatric studies.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

Recommended revisions to the proposed PI are summarized below.

- **Indications and Usage:** The agreed indication statement reads as “LUMISIGHT is indicated for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery.”

LUMISIGHT is a cross-labeled drug-device combination product. The device constituent, Lumicell DVS, is a fluorescence imaging device. Labeling of imaging products, including optical imaging agents, provides imaging type (PET, CT etc.) in the indication statement and imaging instructions including a specific device in a subsection of the DOSAGE AND ADMINISTRATION section. Therefore, the recommended indication statement of LUMISIGHT does not include the specific device, Lumicell DVS, although they are designated as drug-device combination products. Instead, the indication statement includes “fluorescence imaging” as the imaging type that is performed with LUMISIGHT and the detailed information of the imaging device appears in section 2.4 Imaging. This approach is consistent with previously approved optical imaging products.

- **Dosage and Administration:** The recommended dose is 1 mg/kg by IV injection over 3 minutes administered 2 to 6 hours prior to imaging, and the proposed drug product allows withdrawal of 39 mg of pegulicanine per vial after reconstitution. Therefore, in most cases, more than one vial will be needed to administer the recommended dose of 1 mg/kg. To prevent potential medication dosing errors from using multiple vials, the following labeling statements were recommended in the Preparation (2.2) and Administration (2.3) subsections.

2.2 Preparation of LUMISIGHT

Important Preparation Instruction

The recommended dose depends on the individual patient’s weight. Multiple vials of LUMISIGHT may need to be reconstituted to achieve the individual patient dose.

Preparation Instructions

Calculate the dose (1 mg/kg) and the total volume (mL) of LUMISIGHT based on the individual’s weight.

Obtain the number of vials required to administer the patient dose.

2.3 Administration

Withdraw the calculated volume from the appropriate number of vials into one syringe for administration of a dose of 1 mg/kg. Verify that the syringe contains the intended volume.

The drug is reconstituted with 0.45% sodium chloride injection, and the IV line is flushed with 0.9% sodium chloride injection before and after LUMISIGHT administration. To prevent use of 0.9% sodium chloride injection for reconstitution, the following cautionary statement, “Only use 0.45% Sodium Chloride Injection, USP for reconstitution of LUMISIGHT to prevent high osmolality,” was added to the Important Preparation Information subsection and “0.45% Sodium Chloride Injection” was bolded in the reconstitution instructions as well as in the cautionary statement to draw the user’s attention.

A fluorescent imaging device is used with LUMISIGHT to detect residual cancer in the lumpectomy cavity. Lumicell DVS, used in the clinical trials of LUMISIGHT, is the only compatible device so far, and LUMISIGHT and Lumicell DVS will be approved as cross-labeled combination products. As a lifecycle consideration of potential future generic products and similar devices intended to be used with LUMISIGHT, the following device characteristics were added after the reference to Lumicell DVS: *“other fluorescence imaging device that is FDA-approved for specific use with pegulicianine in the indicated population. The device provides illumination to excite the fluorescent components of pegulicianine and collects images showing pegulicianine’s fluorescence emission.”*

- **Warnings and Precautions:** A warning for serious hypersensitivity reactions, especially anaphylaxis, was added to the Warnings and Precautions section. Factors with potentially increased risk of the reactions such as history of reaction to contrast media and PEG-containing products were included. Monitoring of patients, availability of emergency resuscitation drugs, equipment, and trained personnel, and administration interruption were added as recommendations to manage these reactions.

In addition, a warning regarding interference with LUMISIGHT imaging from dyes used for sentinel lymph node mapping was added, and a recommendation for not administering such dyes before imaging with LUMISIGHT was included as a mitigation.

- **Boxed Warning and Contraindications:** Based on the incidence of anaphylaxis (4/276) and severity of hypersensitivity reactions reported from the clinical studies, a boxed warning for anaphylaxis and other serious hypersensitivity reactions was added, and contraindication of LUMISIGHT in patients with a history of hypersensitivity reaction to pegulicianine was recommended.
- **Adverse Reactions:** ARs occurring at $\geq 1\%$ in 726 patients (703 breast cancer and 23 other types of cancer) who received one dose of 1 mg/kg of LUMISIGHT were listed as common ARs: hypersensitivity (1.4%) and chromaturia (85%). The ARs were listed by severity of reaction (hypersensitivity before chromaturia) to alert users, and the ARs that represent a common pathophysiology were grouped together. The following ARs were reported as

hypersensitivity in 10 patients (1.4%): 4 anaphylaxis, 3 hypersensitivity, 2 rash, 1 pruritus , and 1 urticaria.

- Clinical Studies: (b) (4)
Section 14 Clinical Studies only included information about the adequate and well-controlled pivotal study.

12. Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not needed for LUMISIGHT.

13. Postmarketing Requirements and Commitment

The currently available data are sufficient to demonstrate a favorable benefit: risk balance for LUMISIGHT and provide adequate support for labeling. In order to refine the estimate of the incidence of anaphylactic reactions and to better characterize the types of hypersensitivity reactions that occur after administration of LUMISIGHT, the Applicant will conduct a required postmarketing study (see statement below). The results of this study might be used to modify presentation of risk information in labeling and could suggest additional risk mitigation strategies.

Conduct a prospective observational study of sufficient sample size to evaluate the incidence of and characterize anaphylactic reactions to Lumisight in adults with breast cancer. A secondary study objective will be to evaluate the incidence of and characterize other serious hypersensitivity reactions. Adverse events of interest should be pre-defined. Study assessments should include assessment of adverse events of interest (including laboratory data as needed), physical examination, and assessment of blood pressure, heart rate, and oxygen saturation before and at multiple timepoints after Lumisight administration. Adjudicate (using an external expert panel) suspected cases of anaphylaxis and serious hypersensitivity reactions.

The Applicant will also conduct enhanced pharmacovigilance as shown below to allow for a more rapid regulatory response should the risk of serious hypersensitivity reactions substantially differ from expectations based on the premarketing data.

- 1) *We request that for Lumisight you submit all serious domestic and foreign cases of hypersensitivity reactions, including anaphylaxis, as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)).*
- 2) *We request that you provide a narrative summary including analysis of all serious cases of hypersensitivity reactions, including anaphylaxis, reported with the use of Lumisight as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first*

3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval date.

Your analyses should include interval and cumulative data relative to the date of approval of Lumisight. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, dose administered, total number of doses received, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

14. Division Director (Clinical) Comments

I concur with the assessments by the review team and with their unanimous recommendation for approval of the new drug application for pegulicianine, a fluorescent imaging prodrug, for adjunctive use in patients with breast cancer for detection of residual cancer within the lumpectomy cavity after resection of the primary tumor during BCS.

Pegulicianine efficacy is demonstrated by the drug's adequate imaging performance for tumor detection in the one adequate and well-controlled trial and by confirmatory data from a study conducted to validate the performance of the device to be used with the drug for fluorescence imaging of the lumpectomy cavity.

Pegulicianine may cause life-threatening hypersensitivity reactions including anaphylaxis. Mitigation of risks posed by these reactions includes the preoperative setting for administration of pegulicianine with availability of emergency personnel and equipment, warnings in the labeling to enhance awareness of risk and need for patient monitoring, post-approval enhanced pharmacovigilance with expedited safety reporting to the Agency, and a postmarketing study requirement to evaluate the incidence and characteristics of hypersensitivity reactions in clinical practice.

I conclude that with the risk mitigation steps to be implemented, the benefit/risk profile of pegulicianine for its intended use is favorable and therefore recommend approval of the NDA.

15. Office Director (or Designated Signatory Authority) Comments

I agree with the Division's recommendation to approve Lumisight 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.

From the benefit/risk standpoint, there is a notable risk of anaphylaxis associated with the use of this drug whereas the benefit can be described as modest or “incremental”, with the latter term being repeatedly mentioned during the MIDAC deliberations and then by the reviewers in this document. Nevertheless, the benefit here does seem to outweigh the risk, especially given the clinical use setting and the proposed mitigation strategies (labeling, PMR etc.)

One of the opinions expressed at MIDAC that deserves additional mention involves the recommendation that the patients potentially exposed to this drug during the lumpectomy are informed that reduction in the risk of reoperation has not been yet demonstrated. The Division considered adding a Limitation of Use to the indication statement in line with such a recommendation but ultimately decided against it because outcome data are usually not required for imaging drug approvals. As a result, the Agency would have to be reasonably proactive in steering the company away from claiming, without providing adequate data, that the use of the drug can lead to reduction in second surgeries.

16. Appendices

16.1. References

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CL0007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>63</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CL0006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>69</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

16.3.1. Summary of Bioanalytical Method Validation and Performance

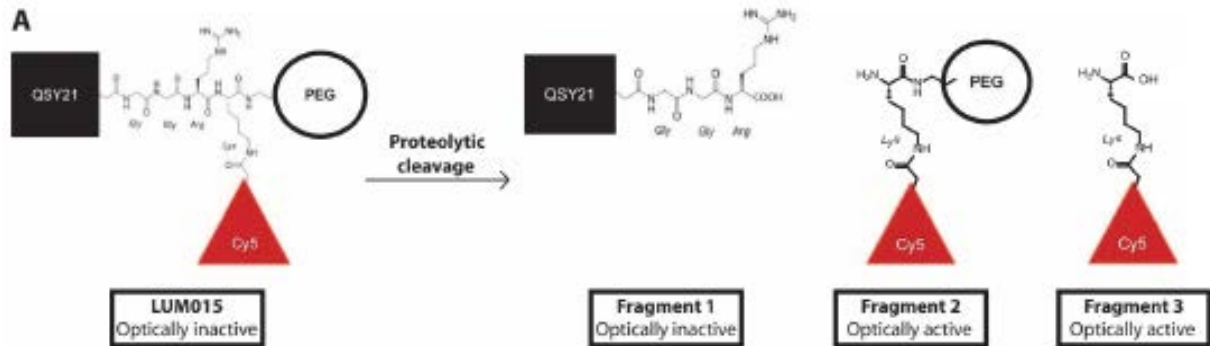
Background

Pegulicianine (LUM015) is composed of a fluorophore (sulfo-Cy5), a dark quencher (QSY21), an amino acid backbone, 2 spacers (Ahx and PEG2), and a 20 kDa methoxy PEG molecule.

Pegulicianine is injected intravenously and accumulates in the tumor microenvironment via cancer-enhanced permeability and retention effects. Pegulicianine is optically inactive (no fluorescence emission) as administered but produces a fluorescent signal after its peptide backbone is cleaved by enzymes (cathepsins and matrix metalloproteases), which have higher activity around the tumor microenvironment. As seen in [Figure 20](#), the following fragment metabolites are generated following proteolytic cleavage of pegulicianine (optically inactive): fragment 1 (optically inactive), fragment 2 (optically active), and fragment 3 (optically active).

Ideally, bioanalytical methods would have been developed and validated for pegulicianine (parent) and its active fluorescent metabolites (fragment 2 and fragment 3).

Figure 20. Depiction of Pegulicianine and Its Fluorescent Metabolites After Proteolytic Cleavage



Source: (Whitley et al. 2016)

Abbreviations: LUM015 = pegulicianine, PEG = polyethylene glycol

Clinical Studies with PK Sampling

The Applicant collected PK in the following 2 studies:

QT Study CLP00201 (healthy subjects)

QT Study CLP00201 used a validated ultra high performance liquid chromatography-tandem mass spectrometry method to determine the PK concentrations of pegulicianine and fragment 3 (fragment 2 was not measured). Method validation parameters are provided in [Table 55](#) and [Table 56](#). Note that pegulicianine did not prolong the QT interval/corrected QT interval, and there were no new safety issues identified following the administration of a single supra-therapeutic dose of up to 4 mg pegulicianine in this study.

Table 55. Bioanalytical Assay Validation Parameters for the Measurement of Pegulicianine in Human Plasma (Used in QT Study CLP00201)

Analytical Validation Report	LML-W7-874	
Short description of method	Affinity purification extraction Reversed-phase UHPLC with MS/MS detection	
Biological matrix	Human plasma	
Anticoagulant	K2EDTA	
Analyte	LUM015 (pegulicianine)	
Internal standard (IS)	Labeled Frag 1	
Calibration concentrations	0.100 µg/mL to 50.000 µg/mL.	
Quality Control (QC) concentrations	0.100 µg/mL, 0.300 µg/mL, 25.000 µg/mL, and 37.500 µg/mL.	
Specificity	No significant interference was observed in all lots of regular blank matrix screened, as well as in lipemic and hemolyzed matrix lots.	
Specificity in the presence of concomitantly administered compounds	No significant interference observed.	
Carryover	Refer to Section 5.2.4. of report	
Lower limit of quantification	0.100 µg/mL Between-run accuracy (%Bias): -2.0% Between-run precision (%CV): 19.4% Within-run accuracy (%Bias): -23.0% - 18.0% Within-run precision (%CV): 6.3% - 10.4%	
Between-run accuracy (%Bias)	-4.8% - 7.7%	
Between-run precision (%CV)	3.7% - 19.4%	
Within-run accuracy (%Bias)	-23.0% - 29.0% (for all five PA runs) -23.0% - 20.0% (for acceptable PA runs) Refer to Section 3 of report.	
Within-run precision (%CV)	1.4% - 10.4%	
Largest run size	189 injections	
Matrix Effect (Calculation of Matrix Factor (MF))	Low QC	High QC
Mean Analyte MF	Mean Analyte MF: 1.0398	Mean Analyte MF: 1.0090
Mean IS MF	Mean IS MF: 1.0559	Mean IS MF: 1.0118
IS Normalized MF	Mean IS-Normalized: 0.9847	Mean IS-Normalized: 0.9973
CV% of IS Normalized MF	%CV: 1.8	%CV: 0.9
Dilution integrity	100.000 µg/mL diluted 5-fold. Accuracy (%Bias): 6.4% Precision (%CV): 7.8%	
Recovery of analyte	54.5 % - 65.2 %	
Short-term stability of the stock solution and working solutions	Confirmed up to 29.2 hours for LUM015 in 0.5% Acetic Acid at 2.003 mg/mL at 4°C nominal. % deviation: 1.8%.	
Long-term stability of the stock solution and working solutions	Confirmed up to 35 days for LUM015 in 0.5% Acetic Acid at 2.003 mg/mL at -20°C nominal. % deviation: -9.0%.	
Short-term stability in biological matrix	Confirmed up to 24.7 hours at 4°C nominal. Accuracy (%Bias): 3.0% for Low Stability QC and -11.8% for High Stability QC.	
Stability in whole blood	Confirmed up to 2.0 hours in an Ice/Water Bath. % deviation: -4.3% for Low QCs and -7.9% for High QCs.	

Source: Table 2 from Applicant's 2.7.1 Summary of Biopharmaceutical Studies and Associated Methods

Abbreviations: CV = coefficient of variation, Frag = fragment, K2EDTA = dipotassium ethylenediaminetetraacetic acid, MS/MS = tandem mass spectrometry, QT = QT interval, UHPLC = ultra-high-performance liquid chromatography

Table 56. Bioanalytical Assay Validation Parameters for the Measurement of Fragment 3 in Human Plasma (Used in QT Study CLP00201)

Analytical Validation Report	LML-W6-126	
Short description of method	Protein precipitation Reversed-phase UHPLC with MS/MS detection	
Biological matrix	Human plasma	
Anticoagulant	K2EDTA	
Analyte	Fragment 3 (fluorescent metabolite Cy5-Lys)	
Internal standard (IS)	Labeled Frag3	
Calibration concentrations	1.00 ng/mL to 200.00 ng/mL.	
Quality Control (QC) concentrations	1.00 ng/mL, 3.00 ng/mL, 100.00 ng/mL and 150.00 ng/mL.	
Specificity	No significant interference was observed in 6 of the 6 regular blank matrix lots screened, as well as in lipemic and hemolyzed matrix lots.	
Specificity in the presence of concomitantly administered compounds	No significant interference observed.	
Carryover	No carryover observed.	
Lower limit of quantification	1.00 ng/mL Between-run accuracy (%Bias): 4.0% Between-run precision (%CV): 7.7% Within-run accuracy (%Bias): 0.0% - 8.0% Within-run precision (%CV): 6.0% - 9.3%	
Between-run accuracy (%Bias)	-5.7% - 4.0%	
Between-run precision (%CV)	2.8% - 7.7%	
Within-run accuracy (%Bias)	-6.0% - 8.0%	
Within-run precision (%CV)	1.5% - 9.3%	
Largest run size	181 injections	
Matrix Effect (Calculation of Matrix Factor (MF))	Low QC Mean Analyte MF: 0.9673 Mean IS MF: 0.9841 Mean IS-Normalized: 0.9805 %CV: 3.1	High QC Mean Analyte MF: 0.9785 Mean IS MF: 0.9597 Mean IS-Normalized: 1.0207 %CV: 1.4
Mean Analyte MF		
Mean IS MF		
IS Normalized MF		
CV% of IS Normalized MF		
Dilution integrity	400.00 ng/mL diluted 5-fold. Accuracy (%Bias): -12.5% Precision (%CV): 7.2%	
Recovery of analyte	88.9 % - 98.4 %	
Recovery of IS	102.0 %	
Long-term stability of the stock solution and working solutions	Confirmed up to 90 days for fragment 3 in Cold MeOH:DMSO 50:50% v/v at 1000.00 µg/mL at 4°C nominal. % deviation: -6.8%. Confirmed up to 90 days for fragment 3 in Cold MeOH:DMSO 50:50% v/v at 0.05 µg/mL at 4°C nominal. % deviation: 9.1%.	
Short-term stability in biological matrix	Confirmed up to 22.5 hours at 4°C nominal. Accuracy (%Bias): -8.3% for Low Stability QC and -9.1% for High Stability QC.	

Source: Table 3 from Applicant's 2.7.1 Summary of Biopharmaceutical Studies and Associated Methods

Abbreviations: CV = coefficient of variation, DMSO = dimethyl sulfoxide, K2EDTA = dipotassium ethylenediaminetetraacetic acid, MeOH = methanol, MS/MS = tandem mass spectrometry, QT = QT interval, UHPLC = ultra-high-performance liquid chromatography

PK Labeling

There is no PK data in Section 12.3 of the LUMISIGHT labeling due to the lack of validated PK parameters in patients with cancer from DUK1-12-137. The only validated PK method was from the QT Study CLP00201 performed in healthy subjects. Since there are not validated PK parameters in patients and there is no mechanistic reason that the PK of pegulicianine and its

active fluorescent metabolites (fragment 2 and fragment 3) should be similar between patients and healthy subjects (pegulicianine is cleaved by enzymes which have higher activity at tumor sites; healthy subjects do not have tumors) (b) (4)

The lack of PK data is not expected to be a safety or efficacy issue for this NDA. Thus, there will not be any associated postmarketing requirements/postmarketing commitments related to this issue.

Phase 1 Study DUK1-12-137 (patients with cancer)

Study DUK1-12-137 used a non-validated high performance liquid chromatography-fluorescence detection method to determine the PK concentrations of pegulicianine, fragment 2, and fragment 3. Because this was the only study in the development program that both collected concentration data and enrolled patients with cancer, there are no validated PK parameters for pegulicianine, fragment 2, or fragment 3 in patients with cancer.

16.4. 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:

4. 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:
 1. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 2. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

16.5. 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.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacology /Toxicology Reviewer	Sunny Awe, PhD	ORDPURM/DPTRDPURM	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Sunny O. Awe -S Digitally signed by Sunny O. Awe -S Date: 2024.04.15 10:57:52 -04'00'			
Supervisory Pharmacologist	Jonathan Cohen, PhD	ORDPURM/DPTRDPURM	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Jonathan E. Cohen -S Digitally signed by Jonathan E. Cohen -S Date: 2024.04.15 11:00:11 -04'00'			
Acting Tertiary Reviewer, Supervisory Toxicologist	Kimberly Hatfield, PhD	ORDPURM/DPTRDPURM	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature: Kimberly P. Hatfield -S Digitally signed by Kimberly P. Hatfield -S Date: 2024.04.15 11:38:09 -04'00'			
Clinical Pharmacology Reviewer	Wenchi (Vicky) Hsu, PhD	OCP/DCPI	Sections: 6, 16.3.1	Select one: ☒ Authored ☐ Approved
	Signature: Wenchi Hsu -S Digitally signed by Wenchi Hsu -S Date: 2024.04.15 10:33:40 -04'00'			
Clinical Pharmacology Team Leader	Christy John, PhD	OCP/DCPI	Sections: 6, 16.3.1	Select one: ☐ Authored ☒ Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S Date: 2024.04.15 10:47:50 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Division Director Clinical Pharmacology	Brian Booth, PhD	OCP/DCPI	Section: 6, 16.3.1	Select one: ☐ Authored ☒ Approved
	Signature: Brian P. Booth -S Digitally signed by Brian P. Booth -S Date: 2024.04.15 10:51:27 -04'00'			
Clinical Reviewer	Gang Niu, MD	OSM/DIRM	Sections: 1, 2, 3, 7, 8	Select one: ☒ Authored ☐ Approved
	Signature: Gang Niu -S Digitally signed by Gang Niu -S Date: 2024.04.15 14:45:44 -04'00'			
Cross Discipline Team Leader/ Clinical Team Leader	Shane Masters, MD, PhD	OSM/DIRM	Authored: 4.1, 4.4, 10, 16.4, 16.5 Approved: All	Select one: ☒ Authored ☒ Approved
	Signature: Shane Masters -S Digitally signed by Shane Masters -S Date: 2024.04.15 14:48:49 -04'00'			
Primary Statistical Reviewer, (DBI)	Sungwon Lee, PhD	OTS/OB/DBI	Sections: 8.3	Select one: ☒ Authored ☐ Approved
	Signature: Sungwon Lee -S Digitally signed by Sungwon Lee -S Date: 2024.04.15 12:10:15 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Secondary Statistical Reveiwer, (DBI)	Jyoti Zalkikar, PhD	OTS/OB/DBI	Sections:8.3	Select one: ☒ Authored ☐ Approved
	Signature: Jyoti Zalkikar -S Digitally signed by Jyoti Zalkikar -S Date: 2024.04.15 12:39:42 -04'00'			
Deputy Division Director, Division of Biometrics I (DBI)	Sue-Jane Wang, PhD	OTS/OB/DBI	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S Date: 2024.04.15 13:04:19 -04'00'			
Associate Director of Labeling (ADL)	Younsook Kim, PharmD	OSM/DIRM	Sections: 11	Select one: ☒ Authored ☐ Approved
	Signature: Younsook Kim -S Digitally signed by Younsook Kim -S Date: 2024.04.15 14:35:32 -04'00'			
Application Technical Lead CMC	Dhanalakshmi Kasi PhD	OPQ/OPQA II	Sections: 4.2	Select one: ☒ Authored ☐ Approved
	Signature: Dhanalakshmi Kasi -S Digitally signed by Dhanalakshmi Kasi -S Date: 2024.04.15 14:23:23 -04'00'			
Supervisory Chemist	Danae Christodoulou, PhD	OPQ/OPQA II	Sections 4.2	Select one: ☐ Authored ☒ Approved
	Signature: Danae D. Christodoulou -S Digitally signed by Danae D. Christodoulou -S Date: 2024.04.15 14:25:30 -04'00'			
Deputy Director Division of Imaging and Radiation Medicine	August Hofling, MD, PhD	OSM/DIRM	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: August Hofling -S Digitally signed by August Hofling -S Date: 2024.04.16 11:37:57 -04'00'			

Director Division of Imaging and Radiation Medicine	Libero Marzella, MD, PhD	OSM/DIRM	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Libero L. Marzella -S Digitally signed by Libero L. Marzella -S Date: 2024.04.16 11:43:37 -04'00'			
Deputy Director Office of Specialty Medicine	Alex Gorovets, MD	OSM	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Alexander Gorovets -S Digitally signed by Alexander Gorovets -S Date: 2024.04.16 11:48:31 -04'00'			

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 15, 2024

FROM: Shane Masters, CDER/OND/OSM/DIRM

SUBJECT: Unireview authorship

APPLICATION/DRUG: NDA 214511 LUMISIGHT (pegulicianine) for Injection

The author for sections 12 and 13 of the Unireview was omitted from the signature page. I authored and approved these sections as CDTL.

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ALEXANDER GOROVETS
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION MEMO

CLINICAL STUDIES

NDA/BLA #: NDA 214511

Supplement #: 9

Drug Name: LUMISIGHT (Pegulicianine)

Indication(s): LUMISIGHT (pegulicianine) for injection is indicated for use in patients with breast cancer to assist in the detection of cancerous tissue within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery. LUMISIGHT is used with Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity.

Applicant: LUMICELL, Inc.

Date(s): 3/17/2023

Review Priority: Priority

Biometrics Division: Division of Biometrics I

Statistical Reviewer: John Lawrence, PhD

Concurring Reviewers: Sue Jane Wang, PhD

Medical Division: Division of Imaging and Radiation Medicine

Clinical Team: Gang Niu, MD, PhD, Primary Clinical Reviewer
Shane Master, MD, PhD, Clinical Team Lead

Project Manager: Alberta Davis Warren

INTRODUCTION

LUMISIGHT (pegulicanine) for injection is indicated for use in patients with breast cancer to assist in the detection of cancerous tissue within the lumpectomy cavity following removal of the primary specimen during lumpectomy surgery. LUMISIGHT is used with Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity.

In Study CL007, there were 62 subjects with positive margins after standard of care surgery that were subsequently LUMISIGHT positive and 25 of those had no residual cancer after LUM-guided shave.

Study CL0007

Study design: Female adults ≥ 18 years with breast cancer undergoing BCS for invasive cancer, DCIS, or a combination of invasive and DCIS. A breast cancer patient has 6 orientations in the breast cavity. Of the 357 patients (device arm, see the figure below), a surgeon proceeds to scan the surgical cavity wall using LUM Imaging Device, records the fluorescence status of each orientation of the cavity (superior, inferior, posterior, anterior, lateral and medial) and removes fluorescence-guided shaves (therapeutic shaves) after standard-of-care lumpectomy.

Orientation level data		Cancer		
		Positive	Negative	Total
Fluorescence	Positive	34	337	371
	Negative	35	1940	1975
	Total	69	2277	2346

Data Sources

\\Cdsub1\evsprod\NDA214511\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\malig-neop-breast\5351-stud-rep-contr\cl0007

This review is focused on the question below:

If LUMISIGHT is not effective, and therefore has an equal chance of being positive for all orientations among all patients regardless of whether cancer is present in the orientation, how many patients would we expect to convert from positive margins after SOC surgery to negative margins after LUM guided shaves, assuming that the number of patients with SOC positive margins ($n=62$), the distribution of SOC positive orientations among patients, and the number of LUM positive orientations after SOC are all the same as was observed in study CL0007? We can also assume that identification of a SOC positive orientation by LUM is sufficient to result in a negative margin for that orientation to simplify the analysis- this was not always the case, but the rate was high enough to justify the assumption.

STATISTICAL EVALUATION

Method 1.

Assume there are 62 patients SOC PM and that 33/62 are LUM POS and 29/62 are LUM NEG. For each of the 33 patients with SOC PM and LUM POS, assume the probability of no residual cancer in the shaves is 25/33 and it is independent of LUM +/-.

For each of the 33 patients that are LUM POS, we simulated a residual cancer in the shaves with probability of no cancer equal to 25/33 and counted the number with no residual cancer. We then simulated 10,000 datasets for these 62 patients and counted the average number across the simulations.

For method 1, the expected number is 25.0.

Method 2.

Assume there are 62 patients SOC PM and that in each orientation there is an equal chance of being positive for all orientations among all patients regardless of whether cancer is present in the orientation. Equal chance meaning that each orientation has the same probability of being LUM positive regardless of whether it has cancer. We will assume the observed LUM positivity rate which is $371/2346 = 15.8\%$ and it is independent across the orientations within a patient and is independent of whether residual cancer is present.

For each of the 62 patients, we simulated the LUM +/- status for each of the 6 orientations. If a patient had at least one + orientation, they are counted as LUM+. Then, for each of the LUM + patients, we simulated a result for whether they have residual cancer. Then, we counted the number of patients who are LUM+ but have no residual cancer. We did this 10,000 times and averaged the number of patients LUM+ with no residual cancer.

For method 2, the expected number of patients with no residual cancer is 30.2.

For both methods, the R program used for the simulation is in the Appendix of this review.

CONCLUSIONS

In study CL0007, there were 62 patients with SOC positive margins. Of those 62 patients, 33 were LUM positive and 25 of those 33 had no residual cancer in the shaves.

This review considered two different methods of estimating the expect number of those 62 patients who would be LUM positive and have no residual cancer in the shaves if LUMISIGHT is not effective, and therefore has an equal chance of being positive for all orientations among all patients regardless of whether cancer is present in the orientation. In the first method, the number LUM positive is fixed at 33 and under those assumptions we used simulation to estimate the expected number that would be free of cancer in the shaves is 25.0. In the second method, the number that is LUM positive is allowed to vary and the LUM +/- status in each orientation for the 62 SOC positive patients as well as the presence of cancer in the shaves is found by simulation. The average number of patients in the simulated data who are LUM positive and have no cancer

in the shaves is 30.2. Therefore, with either of these methods, no evidence is found from the data in this study that LUMISIGHT is effective at identifying patients who have no residual cancer in shaves.

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APPENDICES

Simulation for method 1

```
nsim=10000
set.seed(123)
num.no.resid.cancer=rep(0,nsim)
prob.no.resid.cancer=25/33
for (i in 1:nsim) {
  num.no.resid.cancer[i]=rbinom(1,33,prob.no.resid.cancer)
}
mean(num.no.resid.cancer)
```

Simulation for method 2.

```
nsim=10000
set.seed(456)
num.no.resid.cancer=rep(0,nsim)
prob.no.resid.cancer=25/33
for (i in 1:nsim) {
  orient.pos=matrix(rbinom(62*6,1,371/2346),ncol=6)
  resid.pos=sum(rowSums(orient.pos)>0)
  num.no.resid.cancer[i]=rbinom(1,resid.pos,prob.no.resid.cancer)
}
mean(num.no.resid.cancer)
```

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SUE JANE WANG
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