U.S. FOOD & DRUG ADMINISTRATION

FDA Introductory Remarks

Medical Imaging Drugs Advisory Committee Meeting
March 5, 2024

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Outline

- Product and meeting introduction
- FDA guidance for imaging drug development
  - Indications
  - Trial design
  - Efficacy endpoints
- Optical imaging drug considerations and example of precedent
- Questions and discussion points for the committee

LUMISIGHT (Pegulicianine)

- Drug constituent of a combination product that includes the Lumicell Direct Visualization System device
- Established pharmacologic class: Optical imaging agent
- Applicant: Lumicell
- NDA: 214511
- Proposed indications: 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

Regulatory Definition of Imaging Drugs

Consolidated Appropriations Act, 2023

- Section 3621: Regulation of Certain Products as Drugs
  - Any contrast agent shall be deemed to be a drug and not a device
  - The term "contrast agent" means an article that is intended for use in conjunction with a medical imaging device, and:
    - is a diagnostic radiopharmaceutical, or
    - is a diagnostic agent that improves the visualization of structure or function within the body by increasing the relative difference in signal intensity within the target tissue, structure, or fluid.

Benefit-Risk Assessment

- Section 505 of the Federal Food, Drug, and Cosmetic Act
  - For drug approval, FDA requires evidence that a drug's benefit to patients outweighs its risk
- Purpose of this Advisory Committee Meeting:
  - Discuss evidence of effectiveness of LUMISIGHT
  - Discuss safety risk related to adverse reactions
  - Weigh the above to determine favorable or unfavorable balance

Clinical Indications of Imaging Drugs

- FDA Guidance for Industry: *Developing Medical Imaging Drugs and Biological Products, Part 2: Clinical Indications* (June 2004)
  - Structure delineation
    - e.g., visualization of lesions with abnormal vascularity (gadolinium-based contrast)
  - Functional, physiological, or biochemical assessment
    - e.g., estimation of glomerular filtration rate (Tc99m-pentetate)
  - Disease or pathology detection or assessment
    - e.g., detection of bladder cancer lesions (hexaminolevulinate hydrochloride)
  - Diagnostic or therapeutic patient management
    - e.g., selection of patients with prostate cancer for targeted radioligand therapy (Ga68-gozetotide)

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  - Functional, physiological, or biochemical assessment
    - e.g., estimation of glomerular filtration rate (Tc99m-pentetate)
  - **Disease or pathology detection or assessment (disease detection)**
    - e.g., detection of bladder cancer lesions (hexaminolevulinate hydrochloride)
  - Diagnostic or therapeutic patient management
    - e.g., selection of patients with prostate cancer for targeted radioligand therapy (Ga68-gozetotide)

Determining Effectiveness of Imaging Drugs

- FDA Guidance for Industry: *Developing Medical Imaging Drugs and Biological Products, Part 2: Clinical Indications* (June 2004)
  - Establish accuracy/validity
  - Establish clinical value/usefulness

Disease Detection Indication: Establishing Accuracy/Validity (Diagnostic Performance)

- Clinical outcome data are typically not required
- Compare imaging results against a reference ("truth") standard
  - An independent method of measuring the same variable measured by the investigational drug
  - Should closely approximate the true measurement of the variable measured by the investigational drug
  - May not be feasible to perfectly reflect truth

Disease Detection Indication: Reference Standard

- Histopathology is typically favored for determining the presence of a disease or pathology
  - Systematically obtaining histopathology reference standard information is not always feasible
- Other potential reference standards for a disease or pathology include:
  - Follow-up clinical information
  - Conventional imaging, ideally longitudinal

Disease Detection Indication: Diagnostic Performance Endpoints

- Sensitivity and specificity are typically preferred endpoints
  - Require reference standard information to be collected systematically (true positive, true negative, false positive, false negative)
    - Not aways feasible, particularly for optical imaging drug trials
  - Allow determination of whether test performance is better than chance
    - Depending on the clinical context, lower sensitivity or specificity (below 50%) might be balanced by higher value of the other metric
- Other endpoints include:
  - Disease detection rate
  - False positive rate

Disease Detection Indication: Establishing Clinical Value/Usefulness

- Clinical value of detecting a disease is often already well-established by historical experience
  - If not, clinical value must be demonstrated within efficacy trials
- For optical imaging drugs, determining the added clinical value over standard of care (SoC) surgical treatment is also important

Disease Detection Indication: Optical Imaging Trial Designs

- Intrapatient control design
  - Sequentially perform SoC surgery followed by investigational optical image-guided surgery
  - Efficiently controls for patient, tumor, and surgeon variability
  - Randomization of some patients to a non-investigational imaging arm can reduce bias during SoC surgery
- Parallel arm control design
  - Can be used when sequential intrapatient design is not feasible
  - May be needed if the value of detecting a disease or pathology is not established and clinical outcome data must be collected and analyzed
  - Allows for controlled safety analysis

Example Optical Imaging Drug Precedent: CYSVIEW (hexaminolevulinate hydrochloride)

- Heme precursor that accumulates preferentially in neoplastic cells and forms photoactive porphyrins
- FDA-approved in 2010
- Optical imaging agent indicated for use in the cystoscopic **detection of carcinoma of the bladder**
- Instilled into empty bladder via catheter, retained for one hour, and evacuated prior to cystoscopic examination
- Following SoC white light cystoscopy, blue light cystoscopy is performed to identify red fluorescence in neoplastic lesions

CYSVIEW Trial Design and Endpoints

- Enrolled patients clinically indicated for cystoscopy for known or suspected bladder cancer
- Trials utilized intrapatient control design
  - Patients first underwent SoC white light cystoscopy
  - Blue light cystoscopy was subsequently performed to identify additional fluorescent lesions
- Histopathology was collected as the reference standard for all lesions identified by either white or blue light
  - Negative findings were not systematically captured to allow calculation of sensitivity and specificity
- Primary analysis determined the proportion of patients with additional bladder cancer lesions detected by fluorescence after SoC
- Additional analyses evaluated the frequency of false positive results
- Supported a disease detection indication

LUMISIGHT Trial Design and Endpoints

<u>Consistency within the optical imaging drug class</u>

- Intrapatient control trial design was employed to allow primary analysis of added cancer detection by the drug over standard of care surgery
- Enhanced detection of cancer has been considered a clinically meaningful endpoint for approval of optical imaging drugs seeking disease detection indications, and patient outcome endpoints are typically not required
- Preferred reference standard of histopathology was collected in a systematic fashion
- Evaluation of false positive results was included in detailed assessment of sensitivity and specificity

QUESTIONS AND DISCUSSION POINTS FOR THE COMMITTEE

1. DISCUSSION

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

2. DISCUSSION

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

3. VOTE

- Do the benefits of LUMISIGHT 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 LUMISIGHT.

U.S. FOOD & DRUG ADMINISTRATION

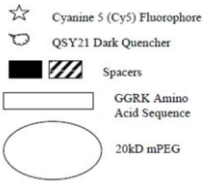
Clinical Overview

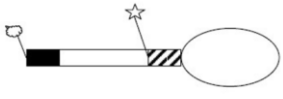
Part One

Shane Masters, MD, PhD
Clinical Team Leader
DIRM, OSM, OND, CDER, FDA

Pegulicianine

- Fluorophore and quencher moieties separated by a peptide linker
- Intact molecule optically inactive
- Cleavage of peptide linker by cancer associated proteases separates fluorophore from quencher

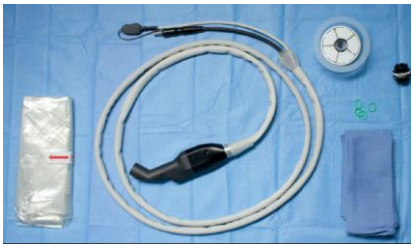




Source: Figure 1 of module 2.6.1 Pharmacology Introduction.
Abbreviations: kD, kilodaltons, mPEG, methoxypolyethylene glycol

Lumicell Direct Visualization System

- Images fluorescence from cleaved LUMISIGHT
- Includes handheld probe capable of imaging within lumpectomy cavity
- Includes a tumor detection algorithm



www.fda.gov Source: Figures 6 and 54 of Lumicell Direct Visualization System Instructions for Use.

Proposed Indication

- 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.

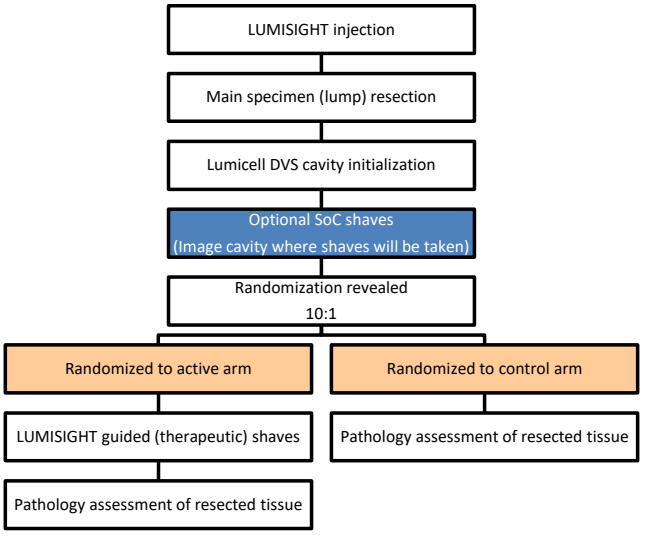
Outline

- Trial design
  - CL0007
  - CL0006
- Key safety results

CL0007

- Prospective study conducted at 14 U.S. sites
- Two-arm, randomized, blinded design to reduce potential surgical bias
- Key patient characteristics
  - Adult females with primary invasive breast cancer with or without ductal carcinoma in situ (DCIS) or DCIS only
  - Scheduled for breast conserving surgery (BCS)
  - No intent to receive neoadjuvant therapy

CL0007 Study Design



Source: Adapted from CL0007 Clinical Study Report Figure 1
Abbreviations: DVS, Direct Visualization System; SoC, standard of care

LUMISIGHT Administration

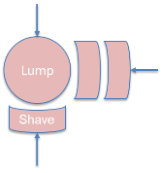
- All patients dosed, regardless of randomization
- 1 mg/kg body weight LUMISIGHT by intravenous route over 3 min
- Administration to occur 2 to 6 hours prior to intraoperative imaging

Surgical Specimens

- Lumpectomy produces a lump (specimen) and creates a cavity in the breast
  - Lump is intended to contain the complete tumor
  - Surfaces of both lump and cavity are divided into 6 orientations: superior, inferior, anterior, posterior, medial, lateral
- Additional specimens may be taken from the cavity as part of standard of care surgery
  - Selective shave: surgeon suspects residual abnormality in the cavity and excises it
  - Comprehensive shave: surgeon systematically removes specimens from all orientations of the cavity
  - No limit to number of shaves taken as standard of care
- After completing standard of care surgery, surgeons take additional specimens from the cavity based on LUMISIGHT result
  - Therapeutic shave: specimen removed because of LUMISIGHT positive imaging
  - Up to 2 therapeutic shaves removed per orientation
- Type and orientation of all specimens recorded
- Histopathologic analysis of specimens performed by local pathologists

Margins

- Each specimen evaluated for (1) presence of cancer and (2) for margin status
- Margin status reflects presence of cancer within a certain distance of the surface that was in contact with the cavity
  - For lumps, all surfaces are relevant and margin status is reported per orientation
  - In patients with invasive cancer, regardless of presence or absence of DCIS, positive margin = 0 mm (“tumor on ink”)
  - In patients with DCIS only, positive margin = within 2 mm deep to the relevant surface
- At orientation-level, margin status defined by the outermost surface (last excised specimen)
- At patient-level, a positive margin at any orientation is positive
- Margin status not definitively known during surgery
  - Can retrospectively assign margin status at varying points in the surgery
    - SoC margin status: after lumpectomy and all standard of care shaves (if taken)
    - LUMISIGHT margin status: after all therapeutic shaves
- Positive margin after completion of surgery is significant risk factor for tumor recurrence



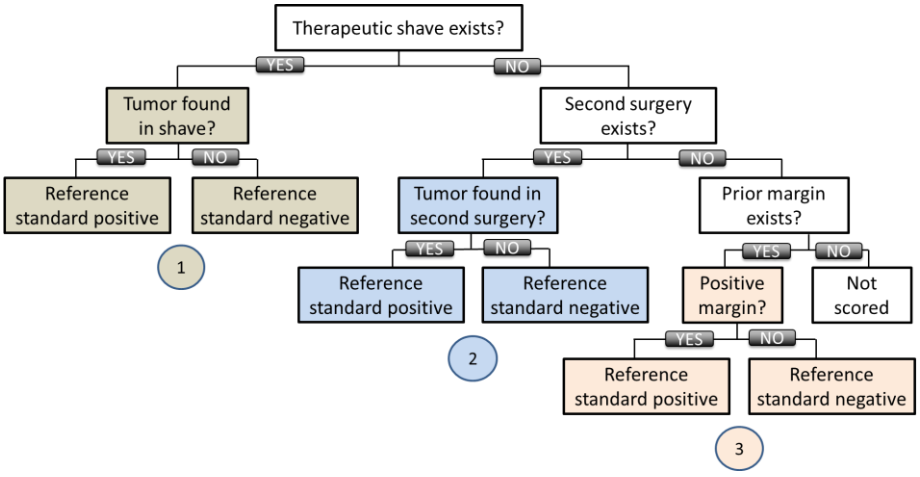
Lumicell DVS Imaging

1. Cavity initialization
   - Obtain images to determine signal intensity threshold for the tumor detection algorithm of the Lumicell Direct Visualization System (DVS)
   - Entire cavity imaged
   - Tumor detection algorithm disabled
2. Prior to SoC shaves
   - Obtain images for exploratory analyses
   - Image orientations where SoC shave is to be taken
   - Tumor detection algorithm disabled
3. After completing SoC surgery
   - Obtain images for main analyses
   - Entire cavity imaged
   - Tumor detection algorithm enabled and shown to surgeon

Tissues, Images, and Orientations

- For tissue-level analyses, a tissue can represent material that is excised from the patient or material that is left in situ
- In most cases, a tissue is represented by one Lumicell DVS image
- Each orientation in each patient usually contributes 0 – 3 tissues
  - Orientations that could not be shaved (i.e., close to skin or chest wall) were not to be imaged
  - Otherwise, # of tissues per orientation was generally # of therapeutic shaves + 1
- Surgeon could combine two orientations into a single image/tissue where necessary

Tissue-Level Reference Standard



www.fda.gov Source: Adapted from CL0007 Clinical Study Report Figure 2

Use of Reference Standard Components

		1	2	3
Hierarchical Assessment	**Total**	**Therapeutic Shaves n (%)**	**Second Surgeries n (%)**	**Prior Margins n (%)**
All tissues	2346	365 (16%)	68 (3%)	1913 (81%)
Reference standard positives	69	34 (49%)	24 (35%)	11 (16%)
Reference standard negatives	2277	331 (15%)	44 (2%)	1902 (83%)

www.fda.gov Source: Adapted from Table 24 of CL0007 Clinical Study Report

Patient Populations

- Safety population
  - Includes all subjects who received LUMISIGHT
- Modified Intent To Treat (mITT) population
  - Includes subjects in the safety population, but excluding subjects who are not able to be imaged with Lumicell DVS
  - Used as the primary analysis population for the three co-primary efficacy endpoints and efficacy analysis of the secondary endpoints
- Per-Protocol population
  - Includes mITT subjects who complete all study evaluations and are without any major protocol deviations that may impact data collection or efficacy analysis
  - Used for sensitivity analysis of the primary and secondary efficacy endpoints

Coprimary Endpoints

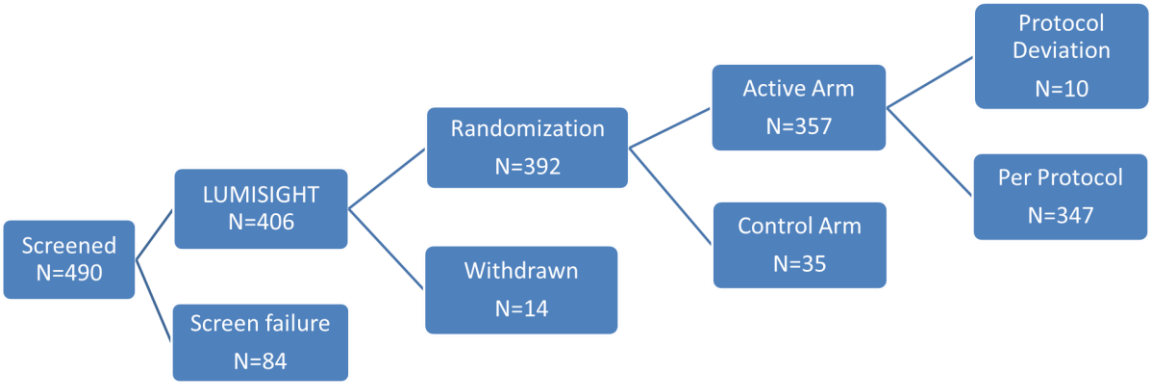
- Patient-level removal of residual cancer
  - Fraction of patients who had cancer found in at least one therapeutic shave among all patients
- Tissue-level sensitivity
- Tissue-level specificity

		Reference Standard	
		Positive	**Negative**
LUMISIGHT imaging result	Positive	A	C
	Negative	B	D
		$Sensitivity = \frac{A}{A+B}$	$Specificity = \frac{D}{C+D}$

Selected Secondary Endpoints

- Conversion rate
  - Proportion of patients with pathology-positive margins after SoC BCS for whom therapeutic shaves resulted in pathology negative margins
  - Calculated among patients with positive margins after SoC BCS and among all patients
- Patient-level sensitivity and specificity
- Volume of specimens removed by therapeutic shaves
- Contribution of therapeutic shave volume to total specimen volume
- Patient satisfaction survey results

Patient Disposition



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

Baseline Characteristics

Characteristics	Safety Analysis Population (N=406)	Modified Intent-to-Treat Population (N=357)	Control Population (N=35)
Tumor histology (biopsy and/or main lumpectomy specimen)			
DCIS Only	78 (19%)	70 (20%)	6 (17%)
IDC ± DCIS	284 (70%)	249 (70%)	25 (72%)
ILC ± DCIS	41 (10%)	35 (10%)	4 (11%)
IDC + ILC	3 (<1%)	3 (<1%)	0
Preoperative lymph node status			
Lymph node (+)	10 (2%)	9 (3%)	1 (3%)
Lymph node (-)	60 (15%)	51 (14%)	7 (20%)
No lymph node biopsy	336 (83%)	297 (83%)	27 (77%)
Receptor status			
ER (+)	378 (93%)	335 (94%)	30 (86%)
PR (+)	311 (77%)	272 (76%)	28 (80%)
HER2 (+)	23 (6%)	20 (6%)	3 (9%)
Triple negative			
Yes	15 (4%)	11 (3%)	3 (9%)

Source: Adapted from Table 18 of CL0007 Clinical Study Report
Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor

SoC Margin Status

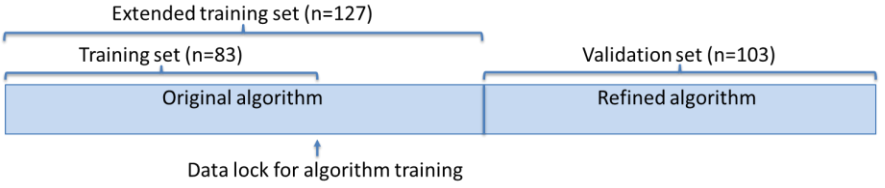
- Margins were positive after SoC surgery (Lump+SoC shaves) in 62/357 (17%) patients
  - Range among the 4 surgeons (of 27 total) who operated on more than 20 subjects in CL0007 was 9% – 18%

Outline

- Trial design
  - CL0007
  - CL0006
- Key safety results

CL0006

- Single-arm, multicenter clinical trial to refine the algorithm used by Lumicell DVS for detection of residual cancer tissue
- At high level, similar design to CL0007
  - Notable exceptions
    - No hypothesis-tested primary endpoints
    - No control arm
    - Tumor detection algorithm updated after interim analysis



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/m2)		
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; Max, maximum; min, minimum; Q, quartile

Baseline Characteristics

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

SoC Margin Status

- Margins were positive after SoC surgery in 15/103 (15%) patients in the validation set
  - 38/230 (17%) in the mITT population

Statistical Designs and Review of Efficacy Results LUMISIGHT (pegulicianine) Lumicell DVS

March 05, 2024
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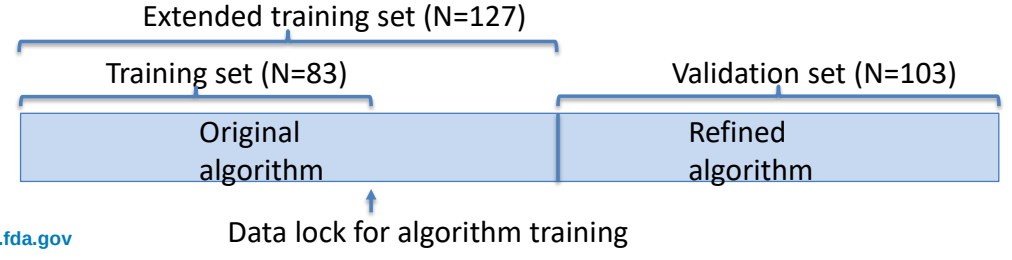
Office of Translational Sciences (OTS)
CDER, US FDA

Outline

- Study CL0006
- Study CL0007
- Summary

Study CL0006

- Study CL0006, a single arm, multicenter feasibility study
- Objective: refine and lock down the imaging detection algorithm used by Lumicell DVS for detection of residual cancer tissue
- The finalized imaging detection algorithm is to be used in Study CL0007 (the primary study for providing evidence of efficacy)
- Study CL0006 is to estimate detection and diagnostic performance of LUMISIGHT, not intended or designed as a controlled study



Removal of Residual Cancer

CL0007 CL0006

	All Refined Algorithm	Validation Set Prospective Refined Algorithm	Extended Training Set Retrospective Refined Algorithm	Training Set Retrospective Refined Algorithm
All subjects	230	103	127	83
Primary endpoint: Ratio of subjects who had residual cancer in at least 1 LUM-guided shave among all subjects in the device arm (subject-level), % (n/N) (95% CI)	11.3 (26/230) (7.5, 16.1)	8.7 (9/103) (4.1, 15.9)	13.4 (17/127) (8.0, 20.6)	14.5 (12/83) (7.7, 23.9)

Prospective refined algorithm was applied during surgery of Study CL0007

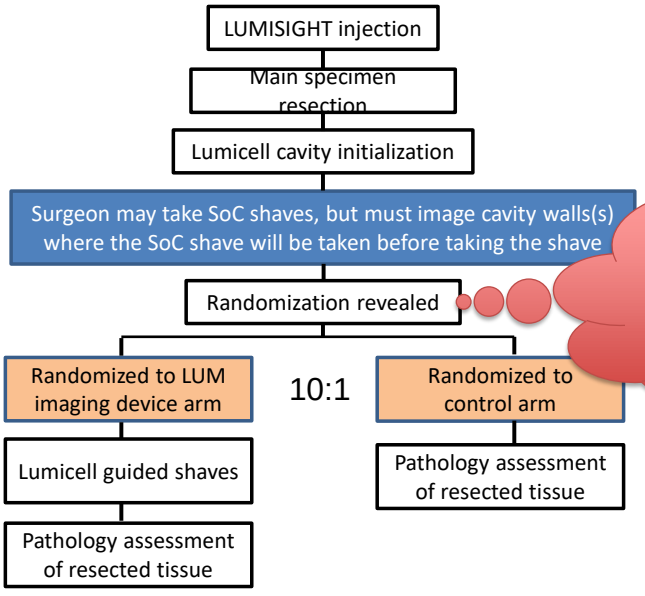
Retrospective: original algorithm used during surgery; post hoc analysis of images using refined algorithm

Tissue-Level Diagnostic Performance

CL0007 CL0006

	Validation Set– Prospective Refined Algorithm (n patients=103)	Extended Training Set–Retrospective Refined Algorithm (n patients=127)
True positive	16	27
False positive	149	301
False negative	9	10
True negative	545	527
GEE estimator		
Sensitivity (95% CI)	63.5% (41%, 81.4%)	72.9% (56%, 85%)
Specificity (95% CI)	80.2% (75.8%, 84%)	64.6% (60.3%, 68.7%)

Study Design for CL0007



Unlike typical 2-arm parallel design, the purpose of randomization is to minimize potential bias from surgeon's under-calling during SoC BCS

Adult patients with breast cancer receiving standard of care (SoC) breast conserving surgery (BCS).

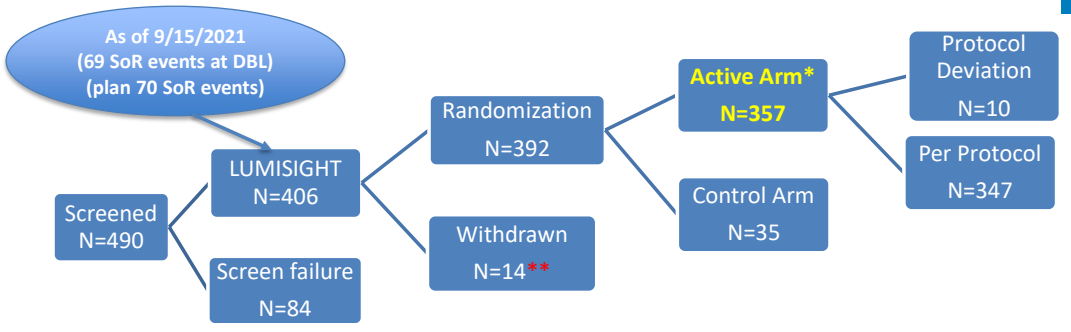
Coprimary Efficacy Endpoints in CL0007

Study CL0007 Coprimary Efficacy Endpoints	P1 (Patient-level) % patients With Residual Cancer Found in ≥ 1 Lumicell Guided Shave	P2 (Tissue-level) Sensitivity	P3 (Tissue-level) Specificity
Success threshold	3%	40%	60%

Sample Size Planning for CL0007

- Targeting success for coprimary endpoints based on feasibility study (CL0006)
- An event-driven design due uncertainty of translating number of reference (truth) standard (SoR) positive tumor tissues to actual number of subjects
- Approximately 268 subjects to target 70 SoR positive tumor tissues for tissue-level sensitivity
- Added 10:1 randomization consideration, estimated 310 total subjects
- Planned maximum is 450 subjects
- Data Safety Monitoring Board (DSMB) monitoring until 70 SoR positive tumor tissues to recommend completion of study accrual

Patient Disposition



* Modified intent-to-treat (mITT) patients at randomization (n=357)

** Withdrawn after the injection but prior to randomization (n=14)

➔ Typically included in ITT and in mITT

*** Failed completion of injection

Among 14 withdrawn patients, a total of 7 subjects were due to adverse events:

1 nausea***

2 extravasation (1***)

3 hypersensitivity***

1 anaphylactic reaction***

Primary Efficacy Endpoint 1: Removal of Residual Cancer

- SoR: postoperative histopathology of surgical specimens with level 1 (therapeutic shave), level 2 (second surgeries), and level 3 (prior margins)
- 27 of 357 patients had residual cancer in at least one LUMICELL-guided shave in the modified intent to treat (mITT) patients (7.6%; 95% CI: 5.0%, 10.8%) level-1 SoR
- *This proportion is 7.3% (95% CI: 4.9%, 10.4%) in intent to treat (ITT) (n=371) patients*
- Lower bound of 95% CI still exceeded pre-specified 3% performance goal

Removal of Residual Cancer

	CL0007	CL0006			
	Treatment Arm	**All Refined Algorithm**	**Validation Set Prospective Refined Algorithm**	**Extended Training Set Retrospective Refined Algorithm**	**Training Set Retrospective Refined Algorithm**
All subjects	357	230	103	127	83
Primary endpoint: Ratio of subjects who had residual cancer in at least 1 LUM-guided shave among all subjects in the device arm (subject-level), % (n/N) (95% CI)	7.6 (27/357) (5.0, 10.8)	11.3 (26/230) (7.5, 16.1)	8.7 (9/103) (4.1, 15.9)	13.4 (17/127) (8.0, 20.6)	14.5 (12/83) (7.7, 23.9)

Prospective = refined algorithm was applied during surgery

Retrospective = original algorithm used during surgery; post hoc analysis of images using refined algorithm

Primary Efficacy Endpoints 2 and 3: Tissue-Level Diagnostic Performance

		Reference Standard		Total
		Positive	Negative	
LUMISIGHT Imaging Result*	Positive	34	337	371
	Negative	35	1940	1975
Total		69	2277	2346
Diagnostic Performance** (95% Confidence Interval)		Sensitivity 49.1% (36.4%, 61.9%)	Specificity 86.5% (84.5%, 88.3%)	

* Regions of the lumpectomy cavity from which LUMISIGHT-directed shaves were taken contributed more than one image.
** Sensitivity and specificity were calculated using a generalized estimating equation method to account for within-patient correlations.

Tissue-level sensitivity failed to meet its performance goal of 40%
Tissue-level specificity exceeded its performance goal of 60%.

Tissue-Level Diagnostic Performance

	CL0007	CL0006	
	mITT (N Patients=357)	Validation Set– Prospective Refined Algorithm (N Patients=103)	Extended Training Set–Retrospective Refined Algorithm (N Patients=127)
True positive	34	16	27
False positive	337	149	301
False negative	35	9	10
True negative	1940	545	527
GEE estimator			
Sensitivity (95% CI)	49.1% (36.4%, 61.9%)	63.5% (41%, 81.4%)	72.9% (56%, 85%)
Specificity (95% CI)	86.5 (84.5%, 88.3%)	80.2% (75.8%, 84%)	64.6% (60.3%, 68.7%)

FDA Statistical Comments on LUMISIGHT Performance Coprimary Efficacy Endpoints – Study CL0007

- **Removal of residual cancer (27 patients):**
  14 sites with varying detection; lower 95% limit estimate exceeded 3% threshold
- **Tissue-level diagnostic performance**

	Tissue-Level Sensitivity	Tissue-Level Specificity	Tissue-Level Accuracy*
GEE Approach	49.1% (36.4%, 61.9%)	86.5% (84.5%, 88.3%)	
Unadjusted Approach	49.3% (38.0%, 61.6%)	85.2% (83.4%, 86.6%)	84.1% (82.6%, 85.6%)
Success Threshold	40%	60%	

  - Tissue-level prevalence: planned = 6.4%; observed = 2.9% (95%CI: 2.3%, 3.7%)
  - Among 69 SoT tissue positives, 49% tissues used level-1 therapeutic shaves SoT
- **Proposed indication**: for fluorescence imaging in adults with breast cancer as an adjunct for intraoperative detection of cancerous tissue within resection cavity following removal of primary specimen during lumpectomy surgery

*Summary measure, not a pre-specified tissue-level efficacy endpoint, appeared to suggest tissue-level diagnostic performance being better than 50% chance accuracy

Patient-Level Imaging Performance
Secondary Efficacy Endpoints

	Patient-Level Sensitivity	Patient-Level Specificity	Patient-Level Accuracy*
TP>FN>FP>TN	54% (40%, 68%)	57% (51%, 63%)	59% (53%, 64%)
FN>TP>FP>TN	47% (32%, 62%)	57% (51%, 63%)	56% (50.3%, 61%)

*Summary measure, not a pre-specified endpoint, showed slightly better than chance accuracy
Patient-level prevalence: planned = 63.8%; observed = 13.2% (9.8%, 17.1%)

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.

Conversion Rate
Secondary Efficacy Endpoint

- Converter: patients with pathology-positive margins after SoC BCS for whom therapeutic shaves resulted in pathology negative margins
- There are 62 out of 357 patients (17.4% with 95%CI: 13.6%, 21.7%) had positive margins after SoC surgery
- 9 converters
  - Conversion rate among patients with positive margins after SoC BCS:
    14.5% (=9/62); 95%CI: 6.9%, 25.8%*
  - Conversion rate among all patients:
    2.5% (=9/357); 95%CI: 1.2%, 4.7%*

*Clopper-Pearson method

Summary of Statistical Review on LUMISIGHT Efficacy

- CL0007 met its prespecified threshold on residual cancer detection patient-level efficacy endpoint, and the prespecified threshold on diagnostic tissue-level specificity, but not met on diagnostic tissue-level sensitivity
- Secondary endpoints were not statistically powered, but provided information on patient-level imaging performance and conversion rate among other endpoints to be given in the next FDA clinical presentation
- CL0006 is a feasibility study aimed to finalize the imaging algorithm for detection at tissue level and at patient level, not a controlled study. The estimated detection rate of patient level residual tumor is similar to that observed in CL0007

Thank You

Clinical Overview

Part Two

Shane Masters, MD, PhD
Clinical Team Leader
DIRM, OSM, OND, CDER, FDA

Surgical Specimen Volumes in CL0007

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

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

Patient Satisfaction Scores in CL0007

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

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

Source: Tables 4-2 and 5-2 of Addendum to CL0007 Clinical Study Report
Abbreviation: mITT, modified intent-to-treat

Outline

- Trial design
  - CL0007
  - CL0006
- Key safety results

Integrated Safety Database

- 790 subjects exposed to LUMISIGHT
- Primary safety analysis population
  - 726 patients with cancer of any type who received any amount of LUMISIGHT with intended dose of 1 mg/kg
    - 1 mg/kg = to be marketed dose
    - Subjects without cancer may have less exposure to cleavage products of pegulicianine
  - 703/726 (97%) patients with breast cancer
  - 711/726 (98%) female patients
- Most commonly observed adverse event was chromaturia (85%)

Safety Monitoring

- Most patients in safety database (88%) were enrolled in CL0006 or CL0007
- Safety monitoring was similar in CL0006 and CL0007
  - Standard preoperative, intraoperative, and postoperative monitoring after receipt of LUMISIGHT
    - This can vary across institutions
  - Final safety assessment at the first post-operative visit (no protocol-specified time window)
    - Interview for adverse events
    - Complete blood count (with differential in CL0007) and serum chemistry
  - If allergic reaction observed, obtain histamine, total complement, and tryptase immediately and at 30 min

Hypersensitivity

- Hypersensitivity reactions were the second most commonly observed adverse event (AE), occurring in 4.8% (35/726; 95% confidence interval [CI]: 3.4%, 6.6%)
- 1.4% (10/726; 95% CI: 0.7%, 2.5%) of patients had reactions assessed as related to LUMISIGHT by study investigators
  - Complicating features for attributing causality
    - All subjects in the major studies exposed to LUMISIGHT
    - Numerous other procedures and interventions on day of surgery
- AEs adjudicated as anaphylaxis by FDA occurred in 0.6% of subjects
  - 4/726 (95% CI: 0.2%, 1.4%)

Adverse Events Identified by Hypersensitivity (Broad) FMQ

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 review team; Applicant's Information Request response received January 23, 2024
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.

Characteristics of Hypersensitivity Reactions

Characteristic	Anaphylaxis (n=4)	Other Hypersensitivity (n=31)
Severity	*	
Mild	-	18 (58%)
Moderate	-	12 (39%)
Severe	-	1 (3%)
Life-threatening	-	0
Onset		
During LUMISIGHT injection***	3 (75%)**	2 (6%)
Same day as LUMISIGHT injection	4 (100%)	12 (39%)
Medical therapy administered	4 (100%)	15 (48%)
Study discontinuation	3 (75%)	2 (6%)

* Anaphylactic reactions are by definition systemic and unpredictable and so considered potentially life-threatening.
** The fourth patient experienced symptoms beginning immediately after LUMISIGHT injection.
*** This could only be assessed among cases with narrative information.

RESULTS SUMMARY

Benefit – Primary Efficacy Endpoints

- Removal of additional cancer after standard of care surgery (observed in 8% of subjects (27/357; 95% CI: 5%, 11%) in Study CL007) can be considered clinically meaningful, potentially reducing rates of reoperation and recurrence.
- Sensitivity of 49% (34/69; 95% CI: 36%, 62%) and specificity of 87% (1940/2277; 95% CI: 85%, 88%) for removal of additional cancer at the tissue-level provide a direct assessment of diagnostic performance and demonstrate better than chance accuracy, thereby supporting the patient-level cancer removal coprimary endpoint described above.
- These endpoints are consistent with FDA imaging drug guidance for providing evidence of effectiveness for a disease detection indication. Therefore, for the proposed indication, evaluation of patient outcome endpoints is not required.

Benefit – Secondary Efficacy Endpoints

- Among the 62 patients with margins positive for cancer following standard of care surgery, conversion to all negative margins after LUMISIGHT-guided shaves occurred in 9 patients (15%; 95% CI: 6%, 23%).
  - In all 9 of these patients, LUMISIGHT detected all margins positive for cancer after standard of care surgery.
  - However, in 8 of these 9 patients, no cancer was identified in any LUMISIGHT-guided shaves.
- In 295 patients with all margins negative for cancer following standard of care surgery, LUMISIGHT-guided shaves removed additional cancer in 19 patients (6%; 95% CI: 4%, 9%).

Risk – Anaphylaxis and Serious Hypersensitivity

- Anaphylactic reaction occurred in 0.6% patients in the primary safety analysis population (4/726; 95% CI: 0.2%, 1.4%)
- The peri-operative setting of administration and appropriate labeling are expected to reduce the incidence of serious adverse outcomes related to anaphylaxis risk.
- A PMR study and EPV are expected to further characterize anaphylaxis risk.

Risk Management Considerations

Anil Rajpal, MD, MPH
Deputy Division Director for Safety
DIRM, OSM, OND, CDER, FDA

Outline

- Safety Concerns and Uncertainties
- Risk Management Approaches and Limitations
  - Labeling
  - Postmarketing Requirement (PMR) Safety Study
  - Enhanced Pharmacovigilance (EPV)
  - Risk Evaluation and Mitigation Strategies (REMS) with Elements to Assure Safe Use (ETASU)
- Summary

SAFETY CONCERNS AND UNCERTAINTIES

Safety Concerns

- Hypersensitivity Reactions including Anaphylaxis:

Overall:	**4.8%** (35/726) [3.4%, 6.6%]*
Related (per Investigator):	**1.4%** (10/726) [0.7%, 2.5%]*
Anaphylaxis:	**0.6%** (4/726) [0.2%, 1.4%]*

*95% Confidence Interval

- Anaphylaxis Cases:
  - Occurrence: during or immediately after LUMISIGHT administration

Uncertainties

- Limited sample size (N=726) makes it difficult to get accurate estimates of incidence of anaphylactic reactions
- Lack of an un-exposed concurrent control group and presence of confounders
- Limited information on how patients were monitored following LUMISIGHT administration
  - What timeframe for monitoring should be recommended?

POSSIBLE RISK MANAGEMENT APPROACHES AND LIMITATIONS

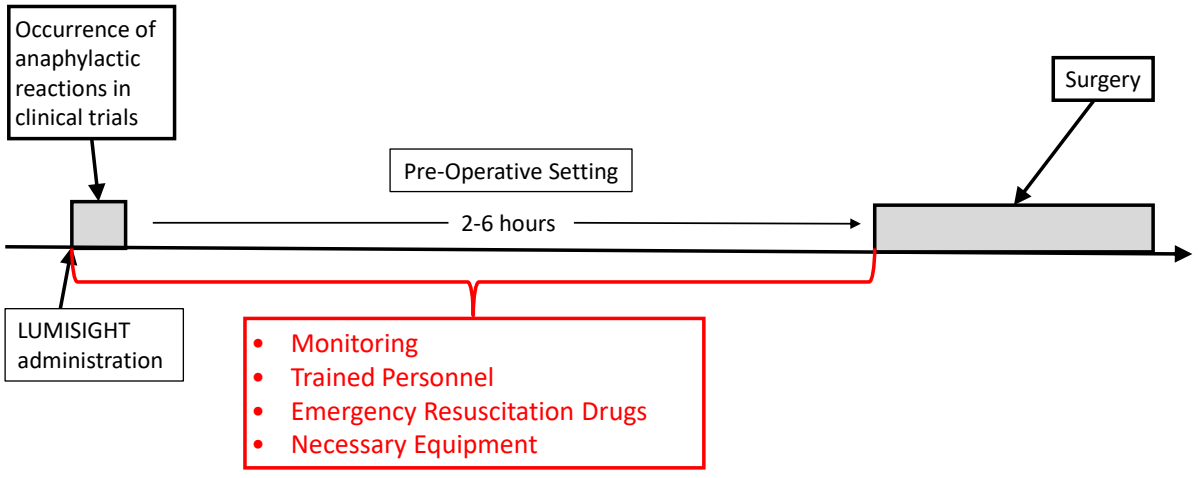
Need for Risk Management

- Administration:
  - 2 to 6 hours before surgery/intraoperative imaging
- Serious hypersensitivity reactions (including anaphylactic reactions):
  - Observed in preoperative setting
  - Time to onset may vary with wider exposure
  - Timeframe for monitoring uncertain

Need for Risk Management (Cont'd)

- Management of serious hypersensitivity reactions (including anaphylactic reactions):
  - Monitoring
  - Immediate availability:
    - trained personnel
    - emergency resuscitation drugs
    - necessary equipment

Need for Risk Management (Cont'd)



Prescribing Information

- Important that the LUMISIGHT Prescribing information (PI) communicate:
  - risk of anaphylaxis and other hypersensitivity reactions
  - need to monitor patients
  - need to have appropriate personnel, medications, and equipment available

Prescribing Information (Cont'd)

- Sections:
  - Warnings and Precautions
  - Boxed Warning
- Limitation:
  - Would not further characterize the risk

Warnings and Precautions*

- "intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are **serious or are otherwise *clinically significant* because they have implications for prescribing decisions or for patient management**."

*FDA guidance for industry "*Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*" (Oct 2011)

Warnings and Precautions (Cont'd)

5.1 Anaphylaxis and Serious Hypersensitivity Reactions

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

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

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

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

Boxed Warning*

- "**adverse reaction so serious** in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is **essential that it be considered in assessing the risks and benefits of using the drug**"

OR

- "serious adverse reaction that can be prevented or **reduced in** frequency or **severity** by **appropriate use of the drug** (e.g., patient selection, **careful monitoring**, avoiding certain concomitant therapy, **addition of another drug** or **managing patients in a specific manner**, avoiding use in a specific clinical situation)"

OR

- "FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "**Risk Evaluation and Mitigation Strategies" Elements to assure safe use**)."

*FDA guidance for industry "*Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format*" (Oct 2011)

Boxed Warning (Cont'd)

WARNING: ANAPHYLAXIS AND SERIOUS HYPERSENSITIVITY REACTIONS

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

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

Considerations for Risk Management

- Several complementary approaches, such as the options listed below, may be considered to mitigate or further characterize adverse events such as hypersensitivity in the postmarket setting.
  - PMR Safety Study
  - EPV
  - REMS with ETASU
- Each of these approaches, described in the subsequent slides, is associated with limitations that should be considered.

PMR Safety Study

- If adequately designed and executed, a PMR safety study could provide real world experience describing
  - **Incidence** of serious hypersensitivity adverse reactions, and
  - **Time to onset** of hypersensitivity adverse events.
- A postmarketing safety study **would not mitigate the risk**

EPV Considerations

- EPV represents a potential approach to **further characterizing a known risk**, such as hypersensitivity reactions, including anaphylaxis
- FDA may request the Applicant to
  - summarize and assess interval and cumulative data for **adverse events of interest** (e.g., hypersensitivity reactions) at a **recurring frequency defined by FDA**
  - submit **expedited 15-day individual case safety reports for certain labeled adverse events of interest**, that are **not otherwise required** by regulation to be submitted as 15-day reports*

*21 CFR 314.80

EPV Considerations (Cont'd)

- EPV would not directly reduce the risk of hypersensitivity
  - may foster **more timely submission of hypersensitivity related safety information** to FDA
  - may allow for a **more rapid regulatory response** if
    - **observed reporting frequency**,
    - **time to onset**, or
    - **clinical severity** of hypersensitivity reactions

    greater than or different from what is described in product labeling

Considerations for REMS With ETASU

- If additional risk mitigation strategies beyond labeling are **necessary to ensure the benefits** of LUMISIGHT **outweigh the risk** of anaphylaxis, a REMS with ETASU can:
  - **Restrict administration** of LUMISIGHT to **healthcare settings that are certified in the REMS**

Considerations for REMS With ETASU (Cont'd)

- As part of the certification, healthcare settings would be required to have policies and procedures to support monitoring and management of anaphylaxis
  - Each patient using the drug would be subject to certain **monitoring during the period of greatest risk**
  - Patients are **counseled about the risk and symptoms** of anaphylaxis, and **what to do if symptoms occur**
- This type of REMS would impose **administrative burden** on the healthcare system

SUMMARY

Summary

Labeling

- Would **mitigate the risk** through communication of the risk
- Would not further characterize the risk

PMR

- Can **further characterize the risk** (incidence and time to onset of anaphylaxis and hypersensitivity reactions; if study well-designed/executed)
- Would not mitigate the risk

Summary (Cont'd)

EPV

- **May** help to **further characterize the risk**
- **May** allow a **more rapid regulatory response** if case reports provide new information
- Would not directly reduce the risk

REMS with ETASU

- Would **restrict administration** to **settings** with **policies/procedures** to support **monitoring/management** of anaphylaxis
- Would impose **administrative burden**

U.S. FOOD & DRUG ADMINISTRATION

CHARGE TO THE COMMITTEE

QUESTIONS AND DISCUSSION POINTS FOR THE COMMITTEE

1. DISCUSSION

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

2. DISCUSSION

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

3. VOTE

- Do the benefits of LUMISIGHT 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 LUMISIGHT.

U.S. FOOD & DRUG ADMINISTRATION

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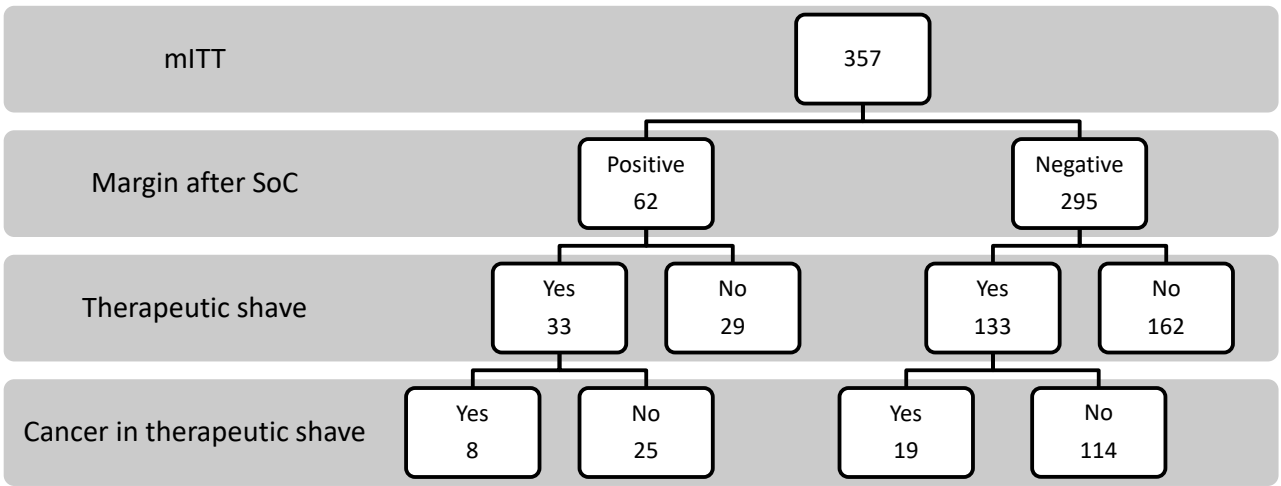
Backup Slides Shown

Medical Imaging Drugs
Advisory Committee Meeting
March 5, 2024

CL0007 Distribution of Patients With Cancer in At Least One Therapeutic Shave



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