CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214511Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Division of Epidemiology I (DEPI-I)
Epidemiology: ARIA Sufficiency

Date:	April 11, 2024
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OPE Deputy Director:	CAPT David Moeny, RPh, MPH, USPHS Office of Pharmacovigilance and Epidemiology (OPE)
OSE Sentinel:	Sarah Dutcher, PhD Sentinel Program
Subject:	ARIA Sufficiency Memo for Anaphylaxis
Drug Name:	Pegulicianine (LUMISIGHT™)
Application Type/Number:	NDA 214511
Applicant/Sponsor:	Lumicell, Inc
Nexus TTT:	2023-6468

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

Medical Product

Pegulicianine (proposed tradename Lumisight) is an optical imaging agent constituent in a combination product consisting of pegulicianine for injection, and a device constituent, the Lumicell Direct Visualization System (DVS). The proposed indication is "for fluorescence imaging in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery." Lumisight is a new molecular entity which contains a fluorophore and a quencher connected by a peptide backbone. Lumisight is optically inactive as administered and produces a fluorescent signal after its peptide backbone is cleaved by enzymes, including cathepsins and matrix metalloproteases, which have higher activity in and around tumor and tumor-associated cells than normal cells. The fluorescence signal from cleaved pegulicianine is detected by the Lumicell DVS, which displays images and highlights suspected tissue containing cancer.[1]

Data provided by the Applicant to demonstrate effectiveness of Lumisight are derived from two studies, CL0007, considered to be adequate and well-controlled, and CL0006, submitted as confirmatory evidence. CL0007 was a prospective, two-arm, randomized, blinded study that enrolled adult females with primary invasive breast cancer or ductal carcinoma in situ (DCIS) who were scheduled for lumpectomy. All enrolled patients received 1 mg/kg pegulicianine intravenously 2 to 6 hours prior to the scheduled surgery, regardless of randomization to the device arm or control arm (10:1). After completing breast conserving surgery (BCS) according to local standard of care, randomization was revealed to the surgeon. Patients in the device arm had imaging of the resection cavity with the Lumicell DVS and additional resection of Lumisight-positive tissues, while patients in the control arm had no imaging or further resection. Histopathology results from resected tissue served as the reference standard. The primary safety analysis population included 726 patients with cancer, predominantly breast cancer, who received an intended dose of 1 mg/kg pegulicianine. The overall rate of hypersensitivity was 4.8% (35/726) and was composed of anaphylactic reactions at 0.6% (4/726) and other hypersensitivity reactions at 4.3% (31/726).[2]

FDA's Division of Imaging and Radiation Medicine (DIRM) convened a Medical Imaging Drug Advisory Committee (MIDAC) meeting 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 this product. The MIDAC panel voted 16-2 with one abstention in favor of Lumisight (pegulicianine) benefits outweighing its risks.

[1] FDA Briefing Document, NDA 214511/pegulicianine, Medical Imaging Drug Advisory Committee Meeting (MIDAC), March 5, 2024; page 11.
[2] FDA Briefing Document, NDA 214511/pegulicianine, Medical Imaging Drug Advisory Committee Meeting (MIDAC), March 5, 2024; page 7.

1.1. Describe the Safety Concern

During the review of NDA 214511, DIRM and DEPI noted that hypersensitivity reactions, including anaphylaxis, were common in pegulicianine clinical trials, occurring in 4.8% (35/726) of patients. Clinical narratives describing possible cases of anaphylaxis were adjudicated by FDA's Division of Pulmonology, Allergy and Critical Care (DPACC) based on the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[3] The DPACC reviewer determined that anaphylaxis occurred in 0.6% (4/726) of patients and concluded that anaphylactic reactions are by definition systemic and unpredictable, and are considered potentially life-threatening.

Available information for the four cases of anaphylaxis is summarized below:[4]

Table 17. Summary of Reactions Adjudicated by FDA as Anaphylaxis

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

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

DIRM concluded that the risk of serious outcomes associated with hypersensitivity reactions can be addressed with labeling (e.g., by assessing all patients for any history of hypersensitivity reaction to contrast media or products containing polyethylene; by always having emergency resuscitation equipment and trained personnel available; by monitoring all patients for hypersensitivity reactions; and by interrupting administration if a hypersensitivity reaction is suspected).

A boxed warning is planned for Lumisight, as follows:[5]

[3] Division of Pulmonology, Allergy and Critical Care (DPACC) Medical Officer Consultation; Lumisight (pegulicianine) and anaphylaxis; October 23, 2023.
[4] FDA Briefing Document, NDA 214511/pegulicianine, Medical Imaging Drug Advisory Committee Meeting (MIDAC), March 5, 2024; page 35.
[5] FDA Briefing Document, NDA 214511/pegulicianine, Medical Imaging Drug Advisory Committee Meeting (MIDAC), March 5, 2024; page 40.

(b) (4)

[redacted]

1.2. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.3. Statement of Purpose

The purpose of this ARIA memo is to evaluate whether ARIA is sufficient to characterize the safety of pegulicianine regarding the incidence of anaphylaxis and to provide clinical details on adverse event assessment (including laboratory data as needed), physical examination, and assessment of blood pressure, heart rate, and oxygen saturation before and at multiple timepoints after administration of pegulicianine. The goal of a post-market study is signal evaluation, to better estimate the incidence of anaphylaxis and further characterize the clinical characteristics of anaphylaxis and hypersensitivity cases. The results of a post-market study will be used to refine the risk mitigation strategies included in labeling.

1.4. Effect Size of Interest or Estimated Sample Size Desired

Because the interest is in assessing the incidence of anaphylactic reaction after administration of Lumisight to adults with breast cancer, this study will be a single arm prospective study of patients receiving Lumisight. The goal of the study is to better characterize the incidence and clinical characteristics of the anaphylaxis cases, therefore sample size will be a protocol review issue.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

Population

The population of interest is adult patients (18 years of age or older) undergoing lumpectomy for breast cancer. Since Lumisight's proposed indication is not restricted to patients with breast cancer of a particular disease stage, ICD-10 codes can be used to ascertain patients with

breast cancer based on discharge diagnoses. In addition, Common Procedural Terminology (CPT) codes can be used to identify lumpectomy in administrative claims.

2.1 Is ARIA sufficient to assess the intended population?

Yes. ARIA is sufficient to assess the intended population based on ICD-10 codes for diagnosis of breast cancer and CPT codes for lumpectomy in administrative claims.

3 EXPOSURES

3.1 Treatment Exposure(s)

The treatment exposure of interest is pegulicianine, which is administered by injection in the peri-operative setting.

3.2 Comparator Exposure

There is no comparator exposure of interest.

3.3 Is ARIA sufficient to identify the exposure of interest?

Yes. It is expected that billing claims will be available to identify Lumisight.

4 OUTCOME(S)

4.1 Outcomes of Interest

The primary outcome of interest is anaphylaxis. Anaphylactic events should be clinically characterized including vital signs (blood pressure, heart rate, oxygen saturation) and elements from clinical laboratory data (e.g., tryptase levels) and physical examination (e.g., skin involvement, mucosal tissue involvement, bronchospasm, reduced peak expiratory flow, dyspnea, hypotonia).

4.2 Is ARIA sufficient to assess the outcome of interest?

No. ARIA is insufficient for the following reasons.

First, diagnostic codes in administrative claims do not have acceptable positive predictive value (PPV) for anaphylaxis, which is required for the confident evaluation of this outcome. A validation study[6] of anaphylaxis in the FDA's Sentinel system showed that the examined algorithm based on ICD-9 codes had a PPV of 63.1%. A post-marketing study on pegulicianine and anaphylaxis would ascertain outcomes based on ICD-10 codes. These codes also have low PPV (64%) as shown in a recent study[7] using data from a healthcare system in Washington state.

Second, administrative claims do not include information that would allow us to clinically characterize anaphylactic events. To specify, none of the following elements[8] can be ascertained

[6] Walsh, K.E., Cutrona, S.L., Foy, S., Baker, M.A., Forrow, S., Shoaibi, A., Pawloski, P.A., Conroy, M., Fine, A.M., Nigrovic, L.E., Selvam, N., Selvan, M.S., Cooper, W.O. and Andrade, S. Validation of anaphylaxis in the Food and Drug Administration's Mini-Sentinel. Pharmacoepidemiol Drug Saf. 2013; 22:1205-1213.

[7] Bann, M.A., Carrell, D.S., Gruber, S., Shinde, M., Ball, R., Nelson, J.C., Floyd, J.S. Identification and Validation of Anaphylaxis Using Electronic Health Data in a Population-based Setting. Epidemiology. 2021;32(3):439-443.

[8] Sampson H.A. et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 2006, 117(2):391-397.

in claims: acuity of onset, manifestations in the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue, or uvula), dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, hypotonia, syncope, incontinence, crampy abdominal pain, vomiting. To document these elements, findings of focused physical examination are needed but such findings are not available in claims or in the electronic health record data in ARIA.

Third, administrative claims do not include information on some measurements that are needed to clinically characterize anaphylaxis, including heart rate and oxygen saturation before and after administration of Lumisight. Measuring the change in these vital signs (pre and post administration) is a critical component of this study. In addition, repeated measurements at multiple timepoints before and after administration are also needed to ensure that dangerously abnormal values of vital signs are not missed.

5 COVARIATES

5.1 Covariates of Interest

Covariates of interest include concomitant medications, comorbidities, and history of hypersensitivity, PEG allergy or anaphylaxis.

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. ARIA can capture drug and medical history covariates. While a history of PEG allergy cannot be identified in ARIA, the prevalence of this covariate is expected to be low and would have minimal impact on the study results.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

A single arm cohort with incidence rates for study outcomes is needed.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA's design and analytic tools are expected to be sufficient to assess the question of interest.

7 NEXT STEPS

Because ARIA is deemed insufficient, DIRM plans to issue a postmarketing requirement (PMR) to the Applicant for an observational study to gather additional safety data. As stated in the PMR/506B PMC DEVELOPMENT TEMPLATE, a serious safety signal of anaphylaxis has been identified during NDA review for LUMISIGHT.

DIRM plans to issue the following PMR to the Applicant:

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.

PMR/PMC Schedule Milestones
Draft Protocol: 08/2024
Final Protocol: 01/2025
Interim Report #1 : 12/2025
Interim Report #2 : 12/2026
Interim Report #3 : 12/2027
Interim Report #4 : 12/2028
Interim Report #5 : 12/2029
Study Completion: 12/2030
Final Report: 05/2031

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATE GELPERIN
04/11/2024 10:34:49 AM

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04/11/2024 02:02:36 PM

DIVISION OF PULMONOLOGY, ALLERGY AND CRITICAL CARE

MEDICAL OFFICER CONSULTATION

Date:	October 23, 2023
To:	Division of Imaging and Radiation Medicine (DIRM) and Office of Surveillance and Epidemiology (OSE)
From:	Rekha Jhamnani, Medical Officer, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Through:	Miya Paterniti, Clinical Team Leader, DPACC
Through:	Kelly Stone, MD, PhD, Associate Director for Therapeutic Review, DPACC
Subject:	Lumisight (pegulicianine) and anaphylaxis Post-Marketing Requirement (PMR)

General Information

NDA: 214511
Applicant: Lumicell
Drug Product: Lumisight (pegulicianine)
Date Received: September 26, 2023
Desired completion: October 18, 2023
Reviewed: PMR/PMC Development Template
Draft Label
Patient Narratives
CL0007 Pivotal Protocol
CL0006 Feasibility Study Phase C, Clinical Study Report

Introduction

This is a Medical Officer response to the request for consultation from the Division of Imaging and Radiation Medicine (DIRM) and the Office of Safety and Epidemiology (OSE) regarding NDA 214511 (priority review goal date November 17, 2023) for Lumisight (pegulicianine), an injected fluorescence-based drug proposed 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. DIRM is requesting input from DPACC regarding 1) the incidence of anaphylaxis observed during the clinical development program, 2) a post-marketing requirement for anaphylaxis, and 3) anaphylaxis labeling.

DIRM also provide the following specific questions for DPACC's input

Questions:

1. Are the 2006 NIAID/FAAN criteria appropriate for determining whether a suspect event represents anaphylaxis?

2. Adverse event narratives are available for 12 patients, including 6 patients with verbatim terms of allergic reaction or anaphylaxis. Please comment on the number of these patients who should be considered to have had anaphylaxis.
3. We are considering a post-marketing requirement to better define the incidence of anaphylaxis after administration of Lumisight. Would there be utility in performing laboratory assessments such as complement, histamine, or tryptase in cases of suspected anaphylaxis in such a study?
4. What is the possibility that some of these reactions are infusion related reactions (IRRs)? Is there value in obtaining cytokine levels to discriminate these as IRRs? Is it reasonable to investigate slower infusion rates in other studies being conducted?
5. How should the label be modified in order to include the risk of anaphylaxis?

In this consult, the Phase C Feasibility Study (CL0006) with an anaphylaxis sub-study and the pivotal protocol for Lumisight (CL0007) are reviewed. DPACC reviewed patient narratives provided from both studies to adjudicate the incidence of anaphylaxis. DPACC also reviewed one additional case from CL0008 (an ongoing, prospective, multicenter, 2-arm, randomized clinical trial in subjects with breast cancer receiving neoadjuvant therapy); a protocol review is not included as only 11 subjects were enrolled in this study at the time of NDA submission. DPACC's labeling recommendations and responses to DIRM's questions are also provided.

Background

Lumicell engineered LUM015, a fluorescence-based imaging agent that accumulates within and around cells. In regions enriched with cathepsin enzymes, such as cancer cells, LUM015 is altered to produce a fluorescent signal. Once cathepsin enzymes cleave LUM015 at its amino acid backbone, the quencher is released and the fluorescent dye in LUM015 emits detectable fluorescence. A consult was written by DPACC to DMIP in October 2018 regarding Lumisight to provide guidance on assessing for anaphylaxis within the protocol for Study CL0007 (consult from Dr. Rekha Jhamnani, G140195 S22). The Applicant's pivotal protocol (CL0007) notes that in a repeat dose toxicity study in dogs, 0.5 or 10 mg/kg of LUM015 IV once daily for 7 days did demonstrate hypersensitivity in several dogs.

CL0006 Feasibility Study Phase C

CL006 Feasibility Study Phase C was a nonrandomized, open-label study in 234 subjects who received 1 mg/kg of Lumisight. As part of the Feasibility Study Phase C, titled, "Expansion into Multiple Institutions for Training in the Use of the LUM Imaging System for Intraoperative Detection of Residual Cancer in the Tumor Bed of Female Subjects with Breast Cancer", a revision of the study protocol occurred

to include a sub-study to evaluate the potential of LUM015 to induce Type I hypersensitivity in subjects. This was due to one SAE of anaphylaxis that occurred in this main study (see **Patient Narratives** below for more details). Subjects in the Phase C study were adults with primary invasive breast cancer, DCIS, or a combination of the two, confirmed by histologic or cytologic sampling (N=230 dosed). Subjects were excluded in CL0006 if they had a history of allergic reaction to PEG or oral or IV contrast agents. Eighteen subjects were enrolled in the hypersensitivity sub-study across 3 institutions, and the primary objective was to evaluate potential complement activation by LUM015. All 18 study subjects underwent histamine, tryptase, and total complement lab draws in addition to vital signs monitoring pre-dose, and at 15-, 30-, and 60-minutes post-dose. None of the subjects in the sub-study experienced hypersensitivity adverse events. Tryptase and total complement levels were within normal limits. Histamine levels were slightly elevated in all 18 subjects. Detailed results are included in Table 1 of the **Appendix**.

Reviewer Comment: Although the Applicant conducted this sub-study as a part of the Phase C Feasibility Study and although the histamine levels are slightly elevated in all subjects, there is minimal utility of collecting this data in subjects who are not experiencing anaphylaxis. Due to an SAE of anaphylaxis that occurred during this Phase C study, the exclusion criteria were amended from "history of anaphylaxis attributed to any contrast agent or drugs containing polyethylene glycol (PEG) to "history of allergic reaction to any oral or IV contrast agents." For further details regarding this SAE, see **Patient Narratives** *below.*

Pivotal Protocol CL0007

The pivotal protocol for Lumisight is summarized below, focusing on items relevant to hypersensitivity monitoring.

Title: Pivotal Study of the LUM Imaging System for Assisting Intraoperative Detection of Residual Cancer in the Tumor Bed of Female Patients with Breast Cancer

Design: This is a prospective, multicenter, two-arm, randomized (to use of the Lumicell Direct Visualization System (DVS)), blinded safety and efficacy study (all subjects are injected with LUM015)

N= 492 randomized

Dose: 1.0 mg/kg injected over 3 minutes 4 ± 2 hours prior to first image recorded with LUM Imaging system during lumpectomy

Co-primary Endpoints: Ratio of patients who have residual cancer in at least one Lumicell-guided shave among all patients and instrument diagnostic accuracy measured as sensitivity and specificity on per-tissue basis

Key Inclusion Criteria: Subjects must be adults with histologically or cytologically confirmed primary invasive breast cancer, DCIS or primary invasive breast cancer with a DCIS component. Subjects with a history of multiple drug allergies, atopic

subjects, and subjects with atopic syndrome are eligible for the study but should be pre-medicated according to institution standards prior to injection with the LUM015 imaging agent.

Key Exclusion Criteria: History of allergic reaction to polyethylene glycol (PEG) or any oral or IV contrast agents.

Safety: All subjects will be observed to assess the safety of LUM015 with standard preoperative, intraoperative, and postoperative monitoring after receipt of the LUM015 injection. The subject will have a final safety assessment at the first post-operative visit, where a blood draw will occur, and lab values evaluated for clinically significant values that differ from the subject's baseline values. All subjects will continue their enrollment and be followed in the study until their medical team determines that no further surgical intervention is required. If the patient is experiencing an allergic reaction to LUM015, the injection should be stopped immediately and the following lab values should be obtained: histamine, total blood complement, tryptase levels. The blood draw for each of these tests should be done as soon as possible after the start of the reaction and again at 30 minutes post start of the reaction. If an immediate blood draw is not possible, collect a 30-minute blood draw at minimum. Each blood specimen should be processed, packaged, and shipped to the contracted central laboratory for this study. Standing orders should be in place for hypersensitivity or allergic reaction for immediate intervention including administration of diphenhydramine, prednisone, or both. If a study subject develops Grade 3 or greater allergic reaction as defined in CTCAE 5.0, Lumicell should be contacted within 24 hours.

*Reviewer Comment: Of note, all subjects in the study received Lumisight. The exclusion criteria for this protocol were history of allergic reaction to any oral or IV contrast agents (in addition to history of anaphylactic reaction attributed to drugs containing PEG), and this was due to the SAE of anaphylaxis that occurred in CL0006 (See **Patient Narratives** below for details). Although the protocol for CL0007 states that subjects with multiple drug allergies and atopy should be pre-medicated, according to the narratives provided by the Applicant, it does not appear that any subjects with hypersensitivity events were pre-medicated. Standing orders for allergic reactions included diphenhydramine, prednisone, or both but did not include injectable epinephrine which is standard of care for anaphylaxis treatment. Additionally, tryptase level should be drawn as a baseline measurement, and between 30 minutes to 4 hours after the onset of hypersensitivity symptoms.*

Patient Narratives

DPACC was asked to review provided patient narratives and adjudicate for anaphylaxis. The four summarized events listed below are considered anaphylaxis by DPACC according to Sampson's criteria 1 (see Appendix). Sampson's criteria 1 are used, as it cannot be determined whether LUMISIGHT is a known allergen to these patients (first exposure). Two narratives for hypersensitivity that did not meet

criteria for anaphylaxis are also listed. See **Appendix** below for PDF documents containing all patient narratives provided to DPACC.

Anaphylaxis Cases

Subject (b) (6) **(CL0006 Phase C Feasibility Study)**
A 73-year-old female with DCIS of the left breast received 104 mg of LUM015 at 12:36 pm. She was enrolled in Phase C of Lumicell's IDE Feasibility Study. After 1.5-2 minutes, the patient complained of chest tightness and shortness of breath. The research nurse noted that the patient's face and upper body became red and stopped the injection immediately. An anesthesiologist noted the patient was diaphoretic, nauseated and having trouble breathing. The patient also appeared apneic, cyanotic, but had palpable pulses and a generalized rash. The subject had a history of allergy to iodinated contrast agents (hives), but did not meet exclusion criteria of history of anaphylaxis to any contrast agent or drugs containing polyethylene glycol. The Investigator noted it was a Grade 4 anaphylactic reaction. The emergent treatment provided consisted of one minute of assisted ventilation with 10 liters of oxygen via a bag-mask. In addition, Epinephrine 0.2 mg was given IV along with solumedrol 100 mg IV. A second peripheral IV was established. Benadryl 50 mg IV was administered, along with Epinephrine 0.4 mg IV. Another Epinephrine 0.2 mg IV dose was ordered. The MET team was alerted as anesthesia ordered Epinephrine gtt starting at 2 mg/min. The patient was transferred to Medical ICU for Epinephrine gtt, famotidine, dexamethasone, Benadryl as needed and airway monitoring. There, the patient stabilized and was discharged home the following day (b) (6) Lumicell held an *ad hoc* meeting of the DSMB. Two possible mitigation strategies were presented: 1) exclude subjects with pre-existing allergies to oral or IV contrast agents or 2) patients with known history of food allergy or reaction to contrast agents should be pre-medicated with corticosteroids (e.g., methylprednisolone, prednisone) and diphenhydramine prior to LUM015. The DSMB voted unanimously to amend the protocol to exclude subjects with pre-existing allergies to oral and IV contrast agents. Lumicell agreed and protocols were amended to include the following exclusion criteria:

History of allergic reaction to any oral or IV contrast agents

This is in addition to the previous exclusion criteria of history of anaphylactic reaction attributed to drugs containing PEG.

Reviewer Comment: This case meets Sampson's criteria 1 as the patient had erythema of the skin, generalized rash, and respiratory distress soon after receiving LUM015. The patient also had a history of urticaria with iodinated contrast agents. She required epinephrine (several doses) as well as solumedrol, dexamethasone, and Benadryl. The Division agrees this subject experienced anaphylaxis. It was due to this SAE that the Applicant's protocols were amended to include more stringent exclusion criteria with regards to previous allergic reaction to oral/IV contrast agents.

Subject [redacted] **(Study CL0007)**

A 47-year-old white female with invasive ductal carcinoma and DCIS of the left breast. On [redacted], she received a nuclear medicine injection and underwent wire placement in anticipation of breast surgery. Around 1:25 pm, infusion of LUMISIGHT was initiated at a dose of 6.1 mL. Around 1:27 pm, the infusion was discontinued due to an apparent reaction to study drug, the actual volume administered was 2.7 mL. The subject had nausea and vomiting and at 1:30 pm, the subject's pulse was 54 bpm (baseline 54 bpm) and blood pressure was 66/33 mmHg (baseline 113/76 mmHg). She was noted to be hyperemic and had profuse erythema all over her body with no 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 500 mL of normal saline, IV Zofran (4 mg) and IV Benadryl (25 mg). By 1:50 pm, the subject fully recovered with normalization of vital signs and no symptoms. Blood samples included the following results: Tryptase was elevated at SAE onset 11.5 µg/L and 12.6 µg/L 30 minutes later; baseline tryptase level was not available. Histamine was elevated at SAE onset (52 nmol/L; normal range 0-8 nmol/L) and 30 minutes after (22 nmol/L). This was reported as a Grade 3 SAE of hypersensitivity (allergic reaction), which was changed from the adverse event coding of nausea and vomiting.

Reviewer Comment: This case meets Sampson's criteria 1 (erythema, and hypotension soon after receiving LUMISIGHT infusion). The case is also supported by elevated tryptase levels, although baseline tryptase levels weren't available to properly interpret results. Although it's unclear when the nuclear medicine injection occurred in reference to the LUMISIGHT injection and reaction onset, since the reaction occurred during the LUMISIGHT infusion we consider LUMISIGHT as the casual trigger.

Subject [redacted] **(Study CL0007)**

A 40-year-old white female with DCIS of the left breast received infusion of LUMISIGHT at 8:07 am on [redacted] (9.1 mL dose). After 1.5 minutes, the infusion was discontinued due to a reaction to study drug; a total of 2.2 mL was administered. She reported shortness of breath, swollen lip, tingling in the tongue, hands, and feet; eye redness; black spots in vision, nausea, and vomiting. Her blood pressure was 110/89 mmHg, pulse was 88 bpm. The subject was treated with IV Benadryl 50 mg and 100 mg of hydrocortisone, as well as ondansetron 4 mg and Pepcid 20 mg. After 20-30 minutes the subject recovered. Histamine levels were elevated at SAE onset (55 nmol/L) and slightly elevated 30 minutes after SAE onset (11 nmol/L). Total complement and tryptase were normal at both timepoints. This was reported as Grade 3 anaphylaxis which was agreed upon by the DSMB and medical monitor.

Reviewer Comment: This case meets Sampson's criteria 1 (shortness of breath and lip angioedema soon after receiving LUMISIGHT infusion); the Division concurs that this reaction is anaphylaxis.

Subject (b) (6) **(CL0008 Feasibility Study)**
A 61-year-old female with invasive ductal carcinoma of the left breast received LUM015 (6.1 ml over 3-minute push). At the completion of the infusion, the patient reported itching and numbing sensation of hands, feet, and lips. No shortness of breath or rash was observed. She was placed in reverse Trendelenburg and given IV fluids. She recovered within 30 minutes. The patient's blood pressure was 64/38 mmHg while experiencing these symptoms (baseline 131/84 mmHg). Three hours later, she went to the PACU and was light-headed and seeing bright lights. She was given ephedrine and placed supine on a bed. She recovered and underwent lumpectomy as planned. Tryptase, histamine, and total complement levels were obtained at 30 minutes and 60 minutes post SAE onset as it was not possible to collect blood samples at symptom onset. All results were normal. This was graded as Grade 3 anaphylaxis and met the criteria of SAE. It was noted in the narrative that vasovagal reaction could not be ruled out, and the Investigator suggested asking study subjects about history of vasovagal reactions/fainting and potentially administering IV fluids preventatively to these patients.

Reviewer Comment: This case meets Sampson's criteria 1 as the subject reported itching and was hypotensive. Although vasovagal reaction was on the differential, the Investigator noted this as Grade 3 anaphylaxis. DPACC agrees this is anaphylaxis. CL0008 is an ongoing, prospective, multicenter, 2-arm, randomized clinical trial in subjects with breast cancer receiving neoadjuvant therapy. DIRM noted that CL0008 was not included in the NDA submission but subjects from this study are included in the 725 subjects analyzed as the safety population by DIRM.

<u>Narratives Labeled as Hypersensitivity but Did Not Meet Anaphylaxis Criteria</u>

Subject (b) (6) **(Study CL0007)**
A 62-year-old white female with IDC of the right breast. At 8:16 am, a slow infusion of 8.5 mL of LUMISIGHT was intended to be given over 3 minutes [was started]. At 8:18 am, the subject had coughed, had difficulty breathing and the infusion was stopped immediately. A total of 4.5 mL of study drug was administered. Facial cyanosis was reported as well as sternal and intercostal muscle retraction. She was given 8 L/minute of oxygen by simple mask. Her oxygen saturation was 91% and blood pressure was 90/50 mmHg with pulse of 88 bpm at 8:25 am (baseline 134/82 mmHg). By 8:34 am, her oxygen saturation was 95%. Her blood pressure was 91/58 mmHg, pulse was 83 bpm, and respirations were 16 breaths/minute. By 8:40 AM, her oxygen saturation (98%), blood pressure (96/61 mmHg), pulse (83 bpm), and respiration (16 breaths/minute) were at baseline levels. 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 subject reported feeling nauseated and Zofran (4 mg/2mL) IV push was administered to the subject at 8:46 AM. At 9:00 AM, blood for clinical laboratory tests was drawn; results were not clinically significant. An ECG performed at 9:51 AM was unremarkable. At 11:36 am on the same day, the

subject underwent mammographic guidance for needle placement in the right breast. She had an episode of feeling faint and passed out briefly, but was spontaneously arousable. She maintained her airway and pulse. This was reported as an adverse event leading to withdrawal (hypersensitivity), and it was noted that the subject had no known allergy to dye.

Reviewer Comment: Although the patient was in severe respiratory distress and hypotensive soon after LUMISIGHT infusion was started, there were no skin or mucosal findings, thus this symptom presentation does not meet Sampson's criteria for anaphylaxis. Despite not meeting formal criteria for anaphylaxis, this case does further raise concern for an anaphylaxis signal as observed in other cases.

Subject (b) (6) **(Study CL0007)**

A 49-year-old white female with IDC of the left breast underwent LUMISIGHT infusion at 8:07 am. After 1.5 minutes she reported dizziness and visual changes described as "dark spots." A total of 6.4 mL of the planned 12.4 mL dose was administered. The subject reported chest pain and the subject's blood pressure was elevated at 196/96 mmHg and her heart rate was 141 bpm. Anesthesia administered 2mg of midazolam IV and 12.5 mg of diphenhydramine IV. The subject recovered and underwent the surgical procedure as planned and was discharged home. Tryptase levels did not result because the plasma was discolored, and the laboratory canceled the testing of these samples. Histamine was elevated to 22 nmol/L and remained elevated at 12 nmol/L 30 minutes later. Total complement levels were normal throughout. The Medical Monitor could not exclude Grade 3 allergic reaction and the event was coded as adverse event leading to withdrawal, hypersensitivity. The patient had a history of walnut allergy and cefaclor allergy.

Reviewer Comment: Although this subject experienced symptoms of syncope with dizziness and visual changes, their presentation does not fit Sampson's criteria due to the lack of skin or mucosal tissue involvement.

Reviewer Comment: The Applicant notes that 848 subjects have received LUM015 and with the Applicant's calculated rate of 4 SAEs of anaphylaxis, they yield a rate of 0.55%. Considering the narratives identified above, including the subject in CLP0008, in a total pool of 725 subjects that received 1 mg/kg of Lumisight (approved dose), this would yield an anaphylaxis rate of 0.55% (4/725). Seven hundred twenty-five subjects were included in the safety population as the following: 709 from breast cancer studies (3 from phase 1 IND study CL0005, 10 from Phase A feasibility study, 45 from Phase B, 234 from Phase C CL0006, 406 from CL0007, and 11 from neoadjuvant feasibility study CL0008). Additionally, the safety population included 12 subjects from a phase 1 soft tissue sarcoma study, 6 from a prostate cancer study, and 38 from gastrointestinal cancer study. Out of these 765 subjects, 725 received the to be approved dose of 1 mg/kg and were deemed the safety population. DIRM noted that other fluorescein-based products do not carry a boxed warning. DIRM would like to request a PMR from the

Applicant to gain more detailed information on the incidence of anaphylaxis with LUM015, and institute a box warning, if necessary, based on the PMR data.

Division Questions/DPACC Responses and Recommendations

1. Are the 2006 NIAID/FAAN criteria appropriate for determining whether a suspect event represents anaphylaxis?

We agree with the use of the 2006 NIAID/FAAN criteria to determine whether a suspect event represents anaphylaxis. These criteria are also referred to as Sampson's criteria and are referenced in the **Appendix** below.

2. Adverse event narratives are available for 12 patients, including 6 patients with verbatim terms of allergic reaction or anaphylaxis. Please comment on the number of these patients who should be considered to have had anaphylaxis.

Four narratives were identified as potential anaphylaxis, see **Patient Narratives** above for details. We confirm the Applicant's anaphylaxis incidence of anaphylaxis rate of 0.55% (4/725).

3. We are considering a post-marketing requirement to better define the incidence of anaphylaxis after administration of Lumisight. Would there be utility in performing laboratory assessments such as complement, histamine, or tryptase in cases of suspected anaphylaxis in such a study?

We have reviewed the draft PMR from DIRM. It was noted through discussion with DIRM that OSE did not think it was feasible to use Sentinel/ARIA to detect postmarketing anaphylaxis, however, their final memo is still under review. Information regarding anaphylaxis risk can be included in the label and could be considered as a boxed warning for this product. DPACC defers the decision to DIRM as to whether a boxed warning is appropriate for this product. DIRM noted that they would like to move forward with a PMR to gather more information regarding the incidence of anaphylaxis with Lumisight.

DPACC worked with DIRM on following PMR example language which was sent to the Applicant on October 6, 2023.

> *Conduct a prospective observational study to evaluate the incidence of anaphylactic reactions after administration of Lumisight to adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following the removal of the primary specimen during lumpectomy surgery. Study assessments should include targeted adverse event assessment, physical examination, and assessment of vital signs (blood pressure, heart rate, and respiratory rate) before and after Lumisight administration. As secondary endpoints, the incidence of other symptoms of hypersensitivity reactions should be estimated.*

Tryptase levels measured within 4 hours of onset of an event that is likely to be a hypersensitivity reaction can be included as supportive data for anaphylaxis; note

that measurement of tryptase up to 30 minutes after a reaction may yield a false positive result since peak levels occur around 2 hours following anaphylaxis. Some patients may have elevated tryptase at baseline, thus a baseline measurement is also recommended, to aid in interpretation of results. Elevations in tryptase are not seen in all episodes of anaphylaxis, so the clinical presentation remains important in diagnosing anaphylaxis. Total complement and histamine can be elevated in the setting of other hypersensitivity events, however, are likely not informative in the setting of anaphylaxis. Total complement levels and histamine are not as specific and can be affected by several different factors[1], for example, histamine has a short plasma half-life. For future or ongoing studies, in addition to an independent data safety monitoring board, we recommend an anaphylaxis adjudication committee.

4. What is the possibility that some of these reactions are infusion related reactions (IRRs)? Is there value in obtaining cytokine levels to discriminate these as IRRs? Is it reasonable to investigate slower infusion rates in other studies being conducted? *(This question was added to the consult via email request*).

Infusion related reactions can share some of the symptom presentations of anaphylaxis (flushing, itching, heart rate and blood pressure changes, dyspnea, back or abdominal pain, fever/chills, nausea/vomiting/diarrhea, rash, hypoxia, seizure, syncope), but are non-IgE mediated. Urticaria, repetitive cough, wheeze, throat tightness, and hypotension are highly suggestive of anaphylaxis. In contrast, fever and muscular pain are not features of anaphylaxis and may be more characteristic of an infusion reaction. Infusion reactions occur more often with monoclonal antibody infusions. The hypersensitivity reactions outlined in the narratives above appear to be more consistent with anaphylaxis as the clinical presentation meets Sampson's criteria and one patient was treated with epinephrine. Drawing cytokine levels during a reaction are not generally useful as the diagnosis relies on clinical symptoms and results of cytokine measurements can be difficult to interpret. It is not unreasonable to explore a slower infusion rate in the Applicant's other studies, however, it may be difficult to make a conclusion that slowing the infusion is reducing the rate of hypersensitivity reactions as the number of events are small. Additionally, due to the symptom presentations in the narratives above, we would not recommend restarting Lumisight at a slower infusion rate or premedicating in patients experiencing a hypersensitivity reaction to the drug for safety reasons[2]. Of note, non-IgE mediated reactions have been reported with radiocontrast media are also a possibility, however, treatment remains the same.[3]

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[1] LoVerde, D et al. Anaphylaxis. *Chest* 153(2): 528-543. February 2018.

[2] Castells, M et al. Infusion Reactions to Systemic Chemotherapy. UpToDate. September 7, 2023.

[3] Anaphylactoid Reactions to Fluorescein. *JACI* 101(6): PS519-S520. June 1998.

Labeling

The Highlights [redacted], and Sections 5.1, 6, and 17 as proposed by the Applicant including DIRM edits are summarized below.

Highlights [redacted]

[redacted]: Serious hypersensitivity reactions, including anaphylaxis, can occur during or following administration. Always have emergency resuscitation drugs and equipment and trained personnel available. Monitor all patients for hypersensitivity reaction. If a hypersensitivity reaction is suspected, immediately [redacted] the injection and initiate appropriate therapy. (5.1)

5.1 [redacted]

[redacted] 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.

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. Always have emergency resuscitation drugs and 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 [redacted] the injection and initiate appropriate therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

[redacted] *[see Warnings and Precautions (5.1)]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LUMISIGHT was evaluated in [redacted] patients who received a single dose of 1 mg/kg of LUMISIGHT. Among these [redacted] patients, [redacted] (97%) had breast cancer and 23 (3%) had other types of cancer. The mean age of patients was 62

years (range: 36 years to 95 years). Distribution by race was 82% White, 7% Black or African American, 6% Asian, and 5% other or unreported. Distribution by ethnicity was 3% Hispanic/Latino, 93% non-Hispanic/Latino, and 4% unknown or unreported.

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

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

17 PATIENT COUNSELING INFORMATION

(b) (4)

Inform patients of the risk of hypersensitivity reactions, including anaphylaxis, and instruct them to (b) (4) if they experience signs and symptoms of a hypersensitivity reaction [see Warnings and Precautions (5.1)].

DPACC Labeling Recommendations

(b) (4)

Warnings and Precautions

- Change heading title to "Anaphylaxis and (b) (4), to highlight that anaphylaxis has occurred with this product.
- Add a statement to advise clinicians to be prepared to treat anaphylaxis to the introduction to Section 5, (b) (4).
- Relocate instructions on how to treat anaphylaxis to this paragraph.
- Since (b) (4) are redundant in describing anaphylaxis, we propose to remove. We also propose to remove (b) (4)

[redacted] We propose to add a statement that [redacted] subjects did not have a history to contrast or PEG to inform providers that a lack of a history of an allergic reaction to contrast or PEG does not preclude patients from having a reaction to LUMISIGHT.

Section 6 and 17 are acceptable from the Division's standpoint.

Proposed labeling language:

Highlights [redacted]

Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, can occur during or following administration. Anaphylaxis has occurred in 4/[redacted] (0.6%) of [redacted] Always have emergency resuscitation drugs, equipment, and trained personnel available. If a hypersensitivity reaction is suspected, immediately discontinue the injection, and initiate appropriate therapy.

5.1 Anaphylaxis and [redacted]

[redacted] Always have emergency resuscitation drugs, equipment and trained personnel available. Monitor all patients for hypersensitivity reactions [redacted] symptom reporting, direct observation, and vital sign measurements. If a hypersensitivity reaction is suspected, immediately discontinue the injection, and initiate appropriate therapy.

[redacted] In clinical studies, 4 [redacted] of [redacted] (0.6%) patients [redacted] 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.

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 [redacted] that experienced anaphylaxis did not have a history of allergic reaction to contrast media or products containing PEG.

Appendix

Table 1 Feasibility Study Phase C Substudy: Tryptase, Total Complement, and Histamine Levels Pre-dose, 15-, 30-, and 60-minutes Post-Dose

	Pre-dose	15 min post	30 min post	60 min post	Mean total (SD)	Reference Range

Tryptase (µg/L) Mean (SD)	4.2 (1.99)	3.8 (1.31)	4.1 (1.73)	4.0 (1.83)	4 (1.7)	≤10.9 µg/L
Total complement (CAE units) Mean (SD)	109.6 (35)	99.6 (38)	103.8 (35)	107.5 (41)	105.3 (36.5)	60-156 CAE units
Histamine (nmol/L) Mean (SD)	15.4 (9.55)	31.6 (43.95)	15.6 (6.44)	12.0 (4.63)	16.7 (18.9)	0-8 nmol/L

Source: Study CL0006 CSR Table 12-7 p. 105

Table I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Sampson et al. Second Symposium on the Definition and Management of Anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium JACI 2006

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KELLY D STONE
10/23/2023 01:53:12 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 27, 2023

To: Alberta Davis-Warren, Regulatory Project Manager, Division of Imaging and Radiation Medicine (DIRM)

Gang Niu, Clinical Reviewer, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LUMISIGHT™ (pegulicianine) for injection, for intravenous use

NDA: 214511

Background:

In response to DIRM's consult request dated April 17, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for Lumisight.

PI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 21, 2023, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on September 26, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 30, 2023
Requesting Office or Division:	Division of Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214511
Product Name, Dosage Form, and Strength:	Lumisight (pegulicianine) For Injection, 40 mg per vial
Applicant/Sponsor Name:	Lumicell, Inc. (Lumicell)
TTT ID #:	2023-4104-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Lumicell, Inc. (Lumicell) submitted revised vial container label and carton labeling for Lumisight (pegulicianine) for injection on August 24, 2023 under NDA 214511. We reviewed the revised vial container label and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Lumicell implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Kane, D. Label and Labeling Review for Lumisight (NDA 214511). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 AUG 17. TTT ID No.: 2023-4104.

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/s/

DEVIN R KANE
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STEPHANIE L DEGRAW
08/30/2023 10:50:35 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 17, 2023
Requesting Office or Division:	Division of Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214511
Product Name, Dosage Form, and Strength:	Lumisight (pegulicianine) For Injection, 40 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Lumicell, Inc. (Lumicell)
FDA Received Date:	March 8, 2023 and July 5, 2023
TTT ID #:	2023-4104
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Lumicell, Inc. (Lumicell) submitted labels and labeling for their marketing application for NDA 214511 for Lumisight (pegulicianine) for injection on March 8, 2023 as part of a rolling submission. Lumisight is an optical imaging agent proposed 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 proposed for use with the Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity. We evaluated the proposed Lumisight prescribing information (PI), vial container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Lumicell, Inc. (Lumicell) provided a rolling submission to obtain marketing approval for Lumisight (pegulicianine) for injection under NDA 214511. We performed a risk assessment of the proposed prescribing information (PI), container label, and carton labeling for Lumisight to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

We note the proposed PI submitted on March 8, 2023 lacked important product quality information including a thawing procedure for the frozen vials, step by step procedure for preparation and administration, and justification for use of 0.45% Sodium Chloride Injection, USP. Thus, the Office of Pharmaceutical Quality (OPQ) sent an information request (IR) on June 22, 2023 to request that the Sponsor submit the additional product quality information. On July

5, 2023, Lumicell submitted the requested product quality information for review. We note the information submitted on July 5, 2023 includes the requested thawing procedure, step by step preparation and administration procedures, and justification for use of 0.45% Sodium Chloride Injection, USP for reconstitution. We defer to OPQ regarding the acceptability of the submitted product quality information.

From a medication error perspective, we note the end user is required to use 0.45% Sodium Chloride Injection, USP for reconstitution of Lumisight and 0.9% Sodium Chloride Injection, USP after administration to flush the IV line. Thus, the potential error exists to reconstitute a vial of Lumisight with 0.9% Sodium Chloride Injection, USP instead of the required 0.45% Sodium Chloride Injection, USP. Per OPQ, there is not a patient safety concern in the event the wrong solution is used for reconstitution. According to Lumicell, in the event the wrong solution is used the final solution will have a higher osmolality (370 mOsmol/L instead of 224 mOsmol/L when reconstituted with 0.45% Sodium Chloride Injection, USP), but the final osmolality will still be less than the upper limit. Based on this information, it was determined that the risk of harm to the patient is minimal if Lumisight is reconstituted with the wrong concentration sodium chloride injection; however, we provide recommendations below for the PI, vial container label, and carton labeling to increase the prominence of the name 0.45% Sodium Chloride Injection, USP to mitigate the risk of reconstitution with the wrong solution.

Our evaluation of the proposed PI, container label, and carton labeling for Lumisight also identified additional areas of vulnerability that may lead to medication errors. For the PI, we recommend including the recommended thawing procedure for the proposed drug product, removing (b) (4) in the PI, and presenting all temperature values in terms of degrees Celsius followed by the Fahrenheit equivalent values in the parentheses. For the vial container label and carton labeling, we recommend presenting all letters of the proposed proprietary name in the same font color, removing (b) (4), additionally we recommend utilizing bold font to differentiate the proposed storage conditions before reconstitution and after reconstitution with 0.45% Sodium Chloride Injection, USP. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Lumisight prescribing information (PI), vial container label and carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Lumicell, Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF IMAGING AND RADIATION MEDICINE (DIRM)

A. General Comments for Highlights of Prescribing Information and Full Prescribing Information

1. We note numeric values are presented throughout the PI with trailing zeros. We recommend removing trailing zeros to avoid misinterpretation of the numeric

value. For example, in the highlights of dosage and administration revise "1.0" to read "1".

2. As currently presented, [redacted] We recommend removing the [redacted]

3. We note [redacted] We recommend including the appropriate units after all numeric values to avoid confusion. For example, in the first bullet under highlights of dosage and administration revise [redacted] to read "2 hours to 6 hours".

4. As currently presented, [redacted] We recommend [redacted] wherever it appears.

5. We note storage temperature ranges are presented in degrees Celsius throughout the PI. We recommend presenting all temperatures in terms of degrees Celsius followed by the Fahrenheit equivalent values presented in parentheses.

B. Highlights of Prescribing Information

1. Highlights of Dosage and Administration

   a. Revise the first bullet under highlights of dosage and administration to read "Recommended [redacted] of Lumisight is 1 mg/kg [redacted] intravenous injection over 3 minutes [redacted] 2 hours to 6 hours prior to imaging.".

   b. [redacted]

2. Highlights of Dosage Forms and Strengths

   a. Revise the highlights of dosage forms and strengths to read "For Injection: [redacted] lyophilized powder in a single-dose vial [redacted]

C. Full Prescribing Information

1. Section 2: Dosage and Administration

   a. Revise Section 2.1 Recommended Dose to read "Recommended [redacted] of Lumisight is 1 mg/kg [redacted] intravenous injection

over 3 minutes [redacted] 2 hours to 6 hours prior to imaging.”.

b. We note Section 2.2 Preparation of Lumisight contains information [redacted] We recommend removing this information from Section 2.2 as it is not needed here.

c. To improve readability and increase the clarity of preparation and administration instructions, we recommend revising Section 2.2 Preparation and Administration of Lumisight to read:

Important Preparation Information

- Prior to reconstitution, store [redacted] vials in the freezer at -25°C to -15°C (-13°F to 5°F). Protect from light.
- Use aseptic technique for the preparation of Lumisight [redacted]
- 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
- Only use 0.45% Sodium Chloride Injection, USP for reconstitution of Lumisight

Preparation Instructions

- Obtain the number of vials required to administer the patient dose.
- Allow the vials to acclimate to room temperature for approximately 5 minutes.
- Reconstitute each [redacted] vial of Lumisight with 4 mL of 0.45% Sodium Chloride Injection, USP [redacted]
- Visually inspect the reconstituted solution. It should be a clear, dark blue colored solution free of particulate matter. Discard if there is any discoloration or particulate matter.
- If not immediately used, store the reconstituted Lumisight vial at room temperature 20°C to 25°C (68°F to 77°F) and use within 4 hours, or store the reconstituted Lumisight vial in the refrigerator at 2°C to 8°C (35°F to 46°F) and use within 24 hours. Protect from light.
- Each vial of Lumisight is for a single-dose. Discard unused portion.

Administration

- Withdraw the calculated [redacted] from the appropriate number of vials into one [redacted] syringe for administration of one single dose.
- Prior to administration of Lumisight, flush the peripheral intravenous (IV) line with 10 mL to 20 mL of 0.9% Sodium Chloride Injection, USP.

- Administer Lumisight as an IV injection over 3 minutes beginning 2 hours to 6 hours prior to imaging.
- After administration of Lumisight, flush the IV line with 10 mL to 20 mL of 0.9% Sodium Chloride Injection, USP.

2. Section 3: Dosage Forms and Strengths

    a. Revise Section 3: Dosage Forms and Strengths to read "For Injection: (b) (4) lyophilized powder in a single-dose vial.".

3. Section 16: How Supplied/Storage and Handling

    a. Revise (b) (4) How Supplied to read "Lumisight (b) (4) in a clear, glass single-dose vial (b) (4) in cartons of 10 vials (NDC 82292-040-10).".

    b. As currently presented, (b) (4) We recommend only including the storage information for the vials prior to reconstitution under one section with the title "Storage and Handling". Revise the storage information to read:

    "Store vials of LUMISIGHT frozen at -25°C to -15°C (-13°F to 5°F) (b) (4) in original carton to protect from light."

4.2 RECOMMENDATIONS FOR LUMICELL, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments for Vial Container Label and Carton Labeling

1. We note (b) (4) We recommend you consider utilizing the one font color for the entire proprietary name in order to improve readability and avoid misinterpretation of the proprietary name.

2. As currently presented, (b) (4) on the proposed vial container label and carton labeling. We recommend (b) (4) on the vial container label needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6). For example, this may be accomplished through increasing the prominence of the critical information (b) (4)

3. We note Lumisight requires reconstitution with 0.45% Sodium Chloride Injection, USP prior to use. Thus, we recommend revising the statement (b) (4) on the proposed vial container label and carton labeling to read "For intravenous use after reconstitution with 0.45% Sodium Chloride Injection, USP" to ensure this important information is not overlooked.

4. We note the proposed vial container label and carton labeling do not contain placeholders for the expiration date and the product lot number. Include a placeholder for the expiration date and lot number. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

B. Vial Container Label

1. We note the proposed vial container label includes the storage information statement (b) (4) We recommend revising the storage information statement to include the appropriate temperature ranges in degrees Celsius followed by degrees Fahrenheit in parentheses. Revise to read "After reconstitution, store at room temperature 20°C to 25°C (68°F to 77°F) and use within 4 hours or store refrigerated at 2°C to 8°C (35°F to 46°F) and use within 24 hours. Protect from light.".

2. As currently presented, (b) (4) on the proposed vial container label. Revise the proposed vial container label to include the statement "Single-Dose vial. Discard unused portion.".

3. We note the vial of Lumisight needs to be protected from light. We recommend including the statement "protect from light" on the proposed vial container label.

C. Carton Labeling

1. We note the top and front panels of the proposed carton labeling include the statement (b) (4) We recommend revising this

statement to read “10 single-dose vials. Discard unused portion.” and removing [redacted]

2. We note the back panel of the proposed carton labeling states [redacted] We recommend revising these statements [redacted]

3. As currently presented, the proposed carton labeling includes the statement [redacted]”. We recommend including the Fahrenheit equivalent values in parentheses after the degrees Celsius values. Additionally, we recommend revising the statement [redacted] and presenting it on the same line as the storage temperature range. Revise to read “Storage: Prior to reconstitution, store frozen at -25°C to -15°C (-13°F to 5°F). Store in original carton to protect from light.”.

4. We note the proposed carton labeling includes the statement [redacted] We recommend revising this statement to read “Recommended Dose: See Prescribing Information”. Additionally, the back panel of the proposed carton labeling includes the statement [redacted] We recommend removing this statement from the proposed carton labeling.

5. As currently presented, the proposed carton labeling includes the reconstitution information statement “Reconstitution: Reconstitute each vial with 4 mL…”. We recommend revising this statement to read “Reconstitution: Reconstitute each vial with 4 mL of 0.45% Sodium Chloride Injection, USP [redacted]

6. We note the proposed carton labeling includes the statement [redacted] We recommend revising to read “After reconstitution: Store vial at room temperature at 20°C to 25°C (68°F to 77°F) and use within 4 hours, or store refrigerated at 2°C to 8°C (35°F to 46°F) and use within 24 hours. Protect from light.”.

7. We note the proposed carton labeling lacks a product identifier. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product’s labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that

the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

APPEARS THIS WAY ON ORIGINAL

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lumisight received on March 8, 2023 from Lumicell, Inc..

Table 2. Relevant Product Information for Lumisight	
Initial Approval Date	N/A
Active Ingredient	pegulicianine
Indication	(b) (4)
Route of Administration	Intravenous
Dosage Form	For Injection
Strength	(b) (4) mg per vial
Dose and Frequency	1 mg/kg (b) (4)
How Supplied	LUMISIGHT (pegulicianine for Injection) (b) (4)
Storage	(b) (4) Store frozen (b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Lumisight labels and labeling submitted by Lumicell, Inc..

- Vial Container Label received on March 8, 2023
- Carton Labeling received on March 8, 2023
- Prescribing Information (Image not shown) received on March 8, 2023, available from \\CDSESUB1\EVSPROD\nda214511\0002\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-labeling-text.pdf

G.2 Label and Labeling Images

- Vial Container Label

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEVIN R KANE
08/17/2023 09:48:25 AM

STEPHANIE L DEGRAW
08/17/2023 10:48:58 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200

Division of Pediatrics and Maternal Health Review

Date: August 7, 2023 **Date consulted:** April 4, 2023

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH, ORPURM, OND

Lynne P. Yao, MD, Division Director, DPMH, ORPURM, OND

To: Division of Imaging and Radiation Medicine (DIRM)

Drug: LUMISIGHT (pegulicianine acetate) injection, 40 mg/vial lyophilized powder

NDA: 214511

IND: 111670

Applicant: Lumicell, Inc.

Subject: Pregnancy and Lactation Labeling Formatting and Recommendations

Proposed Indication: For *in vivo* use in patients with breast cancer to assist in the detection of cancerous tissue within the lumpectomy cavity following the removal of the primary specimen during lumpectomy surgery.

Materials
Reviewed:

- March 8, 2023, New Drug Application for pegulicianine injection for NDA 214511.
- April 26, 2023, DPMH consult for pegulicianine, NDA 214511, DARRTS Reference ID 5164345.

Consult Question: "Please review the PLLR labeling."

1 INTRODUCTION AND BACKGROUND

On March 8, 2023, Lumicell Incorporated submitted the third and final of three rolling submissions to New Drug Application (NDA) 214511, a 505(b)(1) application for LUMISIGHT (pegulicianine acetate) injection, for *in vivo* use in patients with breast cancer to assist in the detection of cancerous tissue within the lumpectomy cavity following the removal of the primary specimen during lumpectomy surgery. The Division of Imaging and Radiation Medicine (DIRM) consulted the Division of Pediatrics and Maternal Health (DPMH) on April 26, 2023, to assist with the Pregnancy and Lactation subsections of labeling.

Pegulicianine is a fluorescence-based imaging agent and is the drug constituent of the LUM Imaging System which is intended for use in vivo following the excision of the main lumpectomy specimen to detect remaining cancer cells after breast surgery. LUMISIGHT is used with the Lumicell Direct Visualization System (DVS) for fluorescence imaging of the lumpectomy cavity.

The sponsor obtained a waiver for conducting animal reproductive studies as part of the NDA submission. The waiver was granted due to the following conditions:[1]

1. Pegulicianine has a short half-life (5.2 hours) and is intended for single use.
2. The intended use population consists of breast cancer patients who are typically undergoing treatment with oncology drugs product prior to or after surgery, and 70-80% are past reproductive age.
3. Lack of genotoxicity.[2] Genotoxicity *in vivo* and *in vitro* studies were negative and phototoxicity studies conducted suggested it was unlikely to be phototoxic *in vivo*.
4. Available non-clinical data from single use rat and repeated-dose rabbit studies indicate no gross or histological findings. The data show that primary or secondary sex organ structures would not be impaired at exposures up to 80 times the plasma exposure margins, and there is no evidence of preferential toxicity for developing organ systems in the fetus or embryo in the event of exposure during pregnancy.

[1] March 30, 2021. Pharmacology/Toxicology IND Assessment and Evaluation review. Sunny Awe, Ph.D., DARRTS Reference ID 111670.
[2] Carcinogenicity studies were not conducted as they are not required for this drug product class.

Table 1. Drug Characteristics and Adverse Reactions and Warnings[3]

Drug Class	Optical Imaging Agent
Mechanism of Action	LUM015 is the developmental name for pegulicianine acetate. LUM015 is inactive in its nominal state; however, in the presence of cancer cells, the cathepsin protease from the tumor cleaves off the cy5 fluorophore to emit detectable fluorescence. The fluorescence is detectable by the LUM Imagine Device that is connected to the computer for display of the images.
Dosage Regimen (proposed)	1 mg/kg intravenous (over 3 minutes) to be administered 2-6 hours prior to imagine
Molecular Weight	20 to 25 kDa
Terminal Plasma Half-life	5.2 hours, appears to be renally excreted
Metabolism	Minimal hepatic metabolism
Volume of distribution	3 to 3.5 L
Adverse Reactions; Warnings and Precautions	Injection related reactions, anaphylaxis, chromaturia

[3] (b) (4) verified by DCN review team.

2 REVIEW

PREGNANCY

Fluorescence-Guided Imaging Agent Exposure during Pregnancy

- LUMISIGHT is a type of fluorescence-guided optical imaging agent. Fluorescent diagnosis is a noninvasive method for imaging precancerous and cancerous tissue. Optical imaging agents use light and other properties of photons to obtain detailed images of tissues and cells within the body reducing a patient's exposure to harmful radiation using non-ionizing radiation, such as ultraviolet and infrared light. Optical imaging does not require the use of ionizing radiation as seen in x-rays and magnetic resonance imaging.[4]
- Fluorescence-guided imaging uses a fluorescent substance along with an imaging device to visualize structures and types of tissue. LUMISIGHT is intended for use along with the Lumicell Direct Visualization System device.
- According to the Center for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), nonionizing radiation exposure during pregnancy is usually not hazardous to pregnant women or their fetus. Radio waves, visible light, computer screens, cell phones and microwaves are all examples of nonionizing radiation.[5,6]
- It is unknown what level of nonionizing radiation is considered safe for pregnant and nonpregnant persons.[5] There are no available clinical guidelines on nonionizing radiation exposure during pregnancy. Optical imaging agents are used with a variety of different types of devices that emit different intensities and amounts of nonionizing radiation. The FDA Guidance for Industry, S10 Photosafety Evaluation of Pharmaceuticals, 2015, provides guidance on recommended international standards for photosafety assessment and harmonizes such assessments that support human clinical trials and marketing authorizations for pharmaceuticals.[7]

Nonclinical Experience

Animal reproductive studies were not conducted for pegulicianine. The sponsor obtained a waiver for conducting animal reproductive studies as part of the NDA submission as described in the introduction and background section above.[1]

Refer to Pharmacology/Toxicology review, DARRTS.

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[4] Optical Imaging. Science Education. National Institute of Health. National Institute of Biomedical Imagine and Bioengineering. https://www.nibib.nih.gov/science-education/science-topics/optical-imaging. Accessed July 1, 2023.

[5] Nonionizing Radiation – Reproductive Health. According to the Center for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), https://www.cdc.gov/niosh/topics/repro/nonionizingradiation.html. Accessed July 1, 2023.

[6] Radiation Basics. United States Nuclear Regulatory Commission. https://www.nrc.gov/about-nrc/radiation/health-effects/radiation-basics.html. Accessed July 1, 2023.

[7] FDA Guidance for Industry, S10 Photosafety Evaluation of Pharmaceuticals, 2015. https://www.fda.gov/media/85076/download.

Review of Literature
DPMH conducted a search of published literature in PubMed and Embase using the search terms "nonionizing radiation and pregnancy," "nonionizing radiation and pregnant women," "nonionizing radiation and pregnancy and birth defects," "nonionizing radiation and pregnancy and congenital malformations," "nonionizing radiation and pregnancy and stillbirth," "nonionizing radiation and spontaneous abortion" and "nonionizing radiation and pregnancy and miscarriage." No relevant data were found in support of this review.

In addition, no pregnancies were reported in the clinical trials with pegulicianine.

Reviewer comment: Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

LACTATION
Nonclinical Experience
Animal reproductive studies were not conducted for pegulicianine. The sponsor obtained a waiver for conducting animal reproductive studies as part of the NDA submission.[1]

Refer to Pharmacology/Toxicology review, DARRTS.

Review of Literature
DPMH conducted a review with regard to nonionizing radiation and lactation, and no data were found. Optical imaging agents are not typically considered hazardous exposures to lactating individuals as the levels of exposure found in common types of nonionizing radiation are usually low.[5]

Reviewer comment: Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Animal reproductive studies were not conducted for pegulicianine. The sponsor obtained a waiver for conducting animal reproductive studies as part of the NDA submission. Part of the approved waiver included review of non-clinical studies that observed primary or secondary sex organ structure would not be impaired at exposures up to 80 times the plasma exposure margins.

Refer to Pharmacology/Toxicology review, DARRTS.

Review of Literature
DPMH conducted a review of available published literature regarding female and male fertility and exposure to nonionizing radiation, and no data were found. Optical imaging agents are not typically considered hazardous exposures and are not expected to have adverse effects on reproduction.

Reviewer comment: Refer to the Discussion/Conclusions section of the review for DPMH's conclusion.

3 DISCUSSION AND CONCLUSIONS

Pregnancy

There are no available human or animal data with pegulicianine exposure during pregnancy. Animal reproduction studies were waived due to the product's short half-life, lack of genotoxicity, intended population also receiving concomitant treatment with oncology products and non-clinical data indicating that primary or secondary sex organ structure would not be impaired at exposures up to 80 times the plasma exposure margins.

DPMH does not recommend a pregnancy registry study and/or a descriptive pregnancy safety study (DPSS) for pegulicianine due to the product's intended patient population with breast cancer who are likely also using oncology products, which are known teratogens, before and right after pegulicianine exposure; therefore, the study results would be difficult to interpret.

Lactation

The presence of pegulicianine acetate in human milk, the effects of pegulicianine acetate on the breastfed infant, and the effects of pegulicianine acetate on milk production are unknown. Pegulicianine has a short half-life and a large molecular weight which suggests minimal potential for drug exposure in the breastfed infant DPMH recommends that subsection 8.2 of labeling include the standard benefit/risk statement for lactation.

DPMH does not recommend a clinical lactation study for pegulicianine acetate as the data collected for this type of study would be difficult to interpret in the intended population given the use of oncologic products immediately before and after exposure of LUMISIGHT.

Females and Males of Reproductive Potential

DPMH recommends omitting subsection 8.3 of the pegulicianine acetate labeling as there are no available human data, and animal reproduction studies were waived because animal studies showed that primary or secondary sex organ structure would not be impaired at substantial doses.

4 LABELING RECOMMENDATIONS

DPMH provided formatting and labeling recommendations for subsections 8.1 and 8.2 of the pegulicianine labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) (see below). DPMH refers to the final NDA action for final labeling.

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE M CERESA
08/07/2023 09:04:33 AM

MIRIAM C DINATALE
08/07/2023 12:56:00 PM

LYNNE P YAO
08/10/2023 02:20:24 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214511
Submission Number	8
Submission Date	3/8/2023
Date Consult Received	4/7/2023
Drug Name	Pegulicianine (LUM015)
Indication	(b) (4)
Therapeutic Dose	1.0 mg/kg administered via peripheral intravenous injection (b) (4)
Clinical Division	DIRM
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 4/7/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 01/23/2021in DARRTS;
- Investigator's brochure (NDA214511 / SDN0002; link);
- Sponsor's protocol #CLP002021 (NDA214511 / SDN0002; link);
- Statistical analysis plan #CLP00201 (NDA214511 / SDN0002; link);
- Cardiac safety report (NDA214511 / SDN0002; link);
- Clinical study report (NDA214511 / SDN0002; link);
- Drafted label (NDA214511 / SDN0002; link);
- QT evaluation checklist (NDA214511 / SDN0006; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA214511 / SDN0006; link).

1 SUMMARY

Pegulicianine did not prolong the QTcF interval in this substitute for thorough QT study – see Table 1 for overall results. The data from the QTc assessment can be used as a substitute for a thorough QT study.

The clinical study CLP00201 was a double-blinded, placebo-controlled single ascending dose study to evaluate the effects of pegulicianine on cardiac repolarization. The highest dose provided 2.7-fold high clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that pegulicianine is associated with increases in the QTcF interval (refer to section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• The intrinsic and extrinsic factors are unlikely to have substantial effect on Cmax. The high clinical scenario is that a delay in surgery time relative to injection of more than 6 hours may prompt the physician to administer a second dose of LUM015. The Cmax at high clinical scenario is projected to be 36.3 µg/mL (section 3.1).
• The Cmax of the maximum dose in this QT study (4 mg/kg, single dose, iv injection) is 99.5 µg/mL which is 2.7-fold of the projected high clinical exposure.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>1 mg/kg</td><td>24.8 µg/mL</td><td>-0.1</td><td>(-2.8 to 2.6)</td></tr>
<tr><td>QTcF</td><td>Two 1 mg/kg injection with 6 hours interval</td><td>36.3 µg/mL</td><td>0.3</td><td>(-2.4 to 3.0)</td></tr>
<tr><td>QTcF</td><td>4 mg/kg</td><td>99.5 µg/mL</td><td>2.5</td><td>(-1.2 to 6.1)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td>Not applicable.</td></tr>
<tr><td>In vivo findings</td><td>Not applicable.</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Pegulicianine did not prolong the QTc interval based on assessment of ECG/PK data from study CLP00201. This assessment can be used as a substitute for a thorough QT study.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

No QT labeling language was proposed by the sponsor in the label submitted to SDN 0002 (link).

Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Pegulicianine (LUM015) is an optical imaging agent 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.

The CS-IRT reviewed the QT assessment proposal previously (DARRTS 01/23/2021). We found the study design and analysis plan adequate to characterize the potential for pegulicianine to prolong the QTc and can potentially serve as a TQT study substitute.

The sponsor conducted a double-blinded, placebo controlled, single ascending dose study in healthy volunteers to evaluate the effects of pegulicianine on cardiac repolarization. The studied doses are a single dose of 0.5, 1, 2, and 4 mg/kg. Each cohort included 8 subjects (6 receiving pegulicianine and 2 receiving placebo). The sponsor's primary endpoint is concentration-QTc. Three models were explored using the concentration of the parent, Fragment 3, and both analytes together. There are no major protocol deviations from our previous review. The sponsor added an additional PK/ECG time point at 10 hr post EOI following our recommendation.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety (link) and our previous review.

Based on proposed label, the recommended dosage of pegulicianine is 1.0 mg/kg administered via peripheral intravenous injection (b) (4), 2 to 6 hours prior to imaging.

In the process of activation of pegulicianine by cathepsin proteases, 3 metabolites are formed: Fragment 1 (inactive metabolite), Fragment 2 (active, fluorescent metabolite) and Fragment 3 (active, fluorescent metabolite). The levels of Fragment 1 and Fragment 2 found in plasma are very low, in the low nM range. The AUC and Cmax of Fragment 3 are all < 10% of the parent drug.

The geometric mean Cmax/dose of pegulicianine was 24.2 (48.8 CV%) kg*µg/mL/mg in a Phase 1 study in cancer patients, and 27.7 (19.5 CV%) kg*µg/mL/mg in a healthy volunteer study. Median (range) Tmax at 4 mg/kg is 0.15 (0.15-1.08) hr for parent and 5.14 (4.12-6.12) hr for Fragment 3. Mean (%CV) terminal half-life is 4.17 (5.0) hr for parent and 5.85 (5.1) hr for fragment 3.

Age, sex, and race are not clinically important intrinsic factors. Pegulicianine is administered only as a single IV dose in a surgical setting; effects of hepatic and renal impairment have not been investigated. Considering that the product is provided as an IV injection for single use with body weight-based dosing, we have agreed in previous review that intrinsic/extrinsic factors are unlikely to have substantial effect on Cmax. Clinically important DDIs are not expected by CYP substrate perpetrators or inducers. In previous clinical pharmacology table (IND 111670/SDN 024, link), the Sponsor proposed that the high clinical exposure scenario for the breast cancer indication would be that a delay in surgery time relative to injection of more than 6 hours may prompt the physician to administer a second dose of LUM015.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	1 mg/kg single dose, IV injection	24.2 µg/mL
Sponsor's High clinical exposure scenario	A second dose administered 6 hours after the first dose due to delay in surgery time for the breast cancer indication	36.3 µg/mL[a]
Highest dose in QT assessment	4 mg/kg single dose, IV injection	99.5 µg/mL
C_{max} Ratio	2.7 (99.5 / 36.3)	

a: calculated by superposition and based on a worst scenario in which a second dose was administered 6 hours after the first dose.

3.1.2 Nonclinical Safety Pharmacology Assessments

ECG and respiratory assessments were conducted in a 7-day intravenous toxicity study in dogs ((b) (4) Study No. 2330-010-001); and heart rate and body temperature evaluations were conducted in a 7-day intravenous toxicity study in rabbits ((b) (4) Study No. 51103-15-205). There were no LUM015-related effects noted on any of the safety pharmacology parameters included in these studies.

No CNS clinical signs were noted in rats with LUM015 or in the 7-day rabbit study in either males or females. It should be noted that blood pressure measurements were not conducted with LUM015; however, there was no indication of any reflex effects on heart rate such as tachycardia or bradycardia as would be expected with a test article related effect on blood pressure. ECGs and heart rates were unaffected in dogs and rabbits, respectively.

Reviewer's comment: No hERG studies are found.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for pegulicianine was based on exposure-response analysis, please see section 3.2.3 for additional details. The sponsor used linear mixed effect model in by-time analysis.

Reviewer's comment: *Given the small sample size for dose group, the reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics. The trend shown in by-time analysis from reviewer's analysis is similar to the trend shown in sponsor's by-time analysis. Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

The sponsor compared the fully automated measurements from the iCOMPAS software to the sponsor's ECG measurement technique EPQT using Bland-Altman (BA) plots. The relationship between the means and differences of the 2 methods was investigated by robust regression using an M estimator. The mean difference in QTcF between the fully automated background QT/RR data using iCOMPAS and the EPQT measurement technique was small across all dose levels, ranging from -1.53 ms (95% CI: -2.001 to -1.065) in the 0.5 mg/kg group to -0.66 ms (95% CI: -0.977 to -0.338) in the 1.0 mg/kg dose group, without relation to dose level.

Reviewer's comment: *The reviewer did not conduct independent bias analysis.*

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<50 or >100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>100 msec and 25% over baseline).

Reviewer's comment: *Reviewer's analysis results are the same with sponsor's analysis results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor used the model recommended in the white paper. Three models were explored using the concentration of the parent, Fragment 3, and both analytes together. The AIC values and slopes from three models are similar. The Sponsor choose full model (both analytes) as independent variables. The results of the sponsor's analysis show an absence of significant QTc prolongation. Our analysis use parent drug concentration only and shown an insignificant slope as well.

Reviewer's comment: *Our analysis is numerically different from the sponsor's analysis because we include parent drug concentration only in the model while the sponsor used the full model as the final model. The conclusion is similar that LUM015 is not associated with* a *significant QTc prolongation effect. Please see Section 4.5 for details.*

3.2.4 Safety Analysis

No deaths, SAEs, severe AEs, or AEs leading to discontinuation in this study. No cardiac disorder AEs were reported. Generally, subjects showed ECG results within the reference range. Occasionally, abnormal ECG assessments were observed, however they were not judged to be clinically significant by the Investigator.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to subject and treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

The reviewer did not conduct bias analysis.

4.3 BY-TIME ANALYSIS

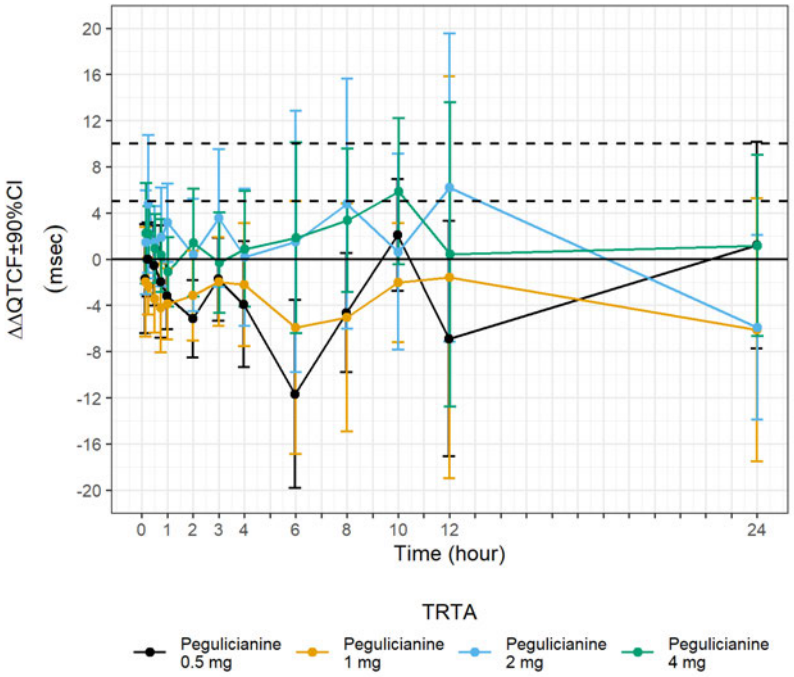
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).



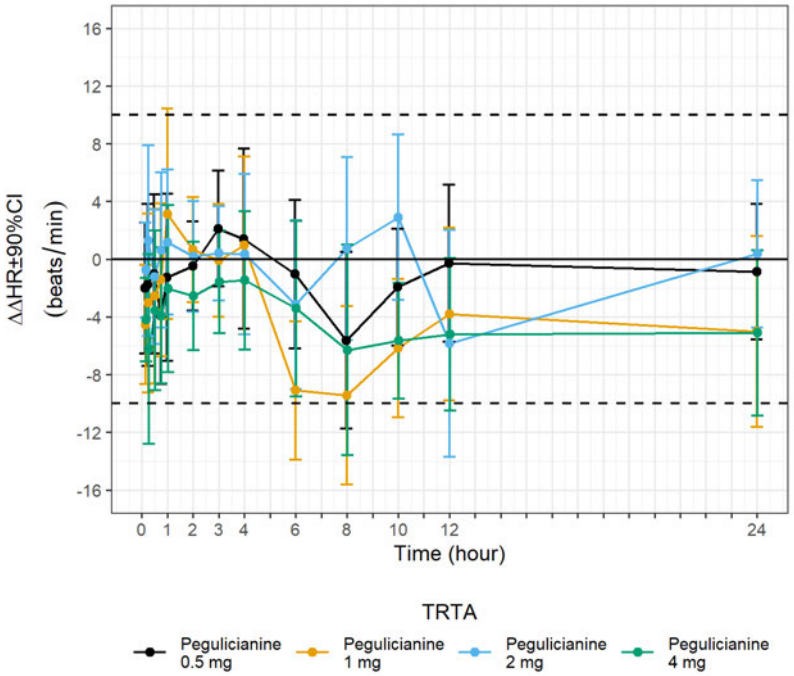
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

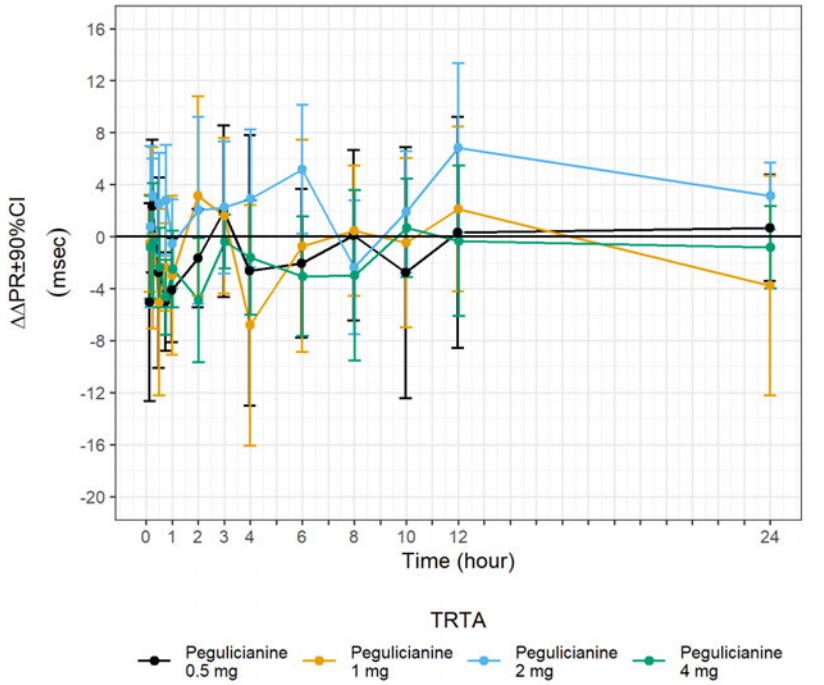
Figure 2: Median and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

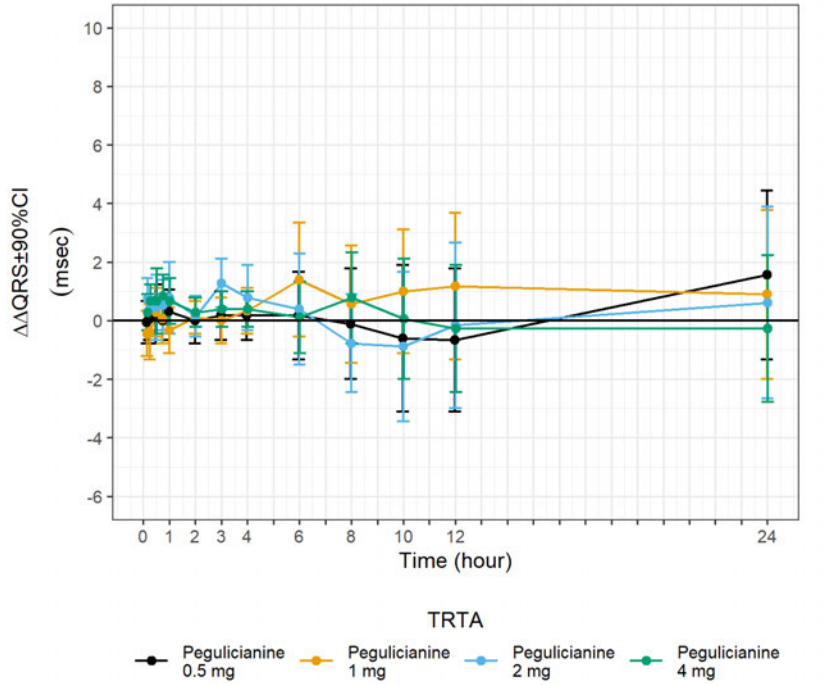
Figure 3: Median and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no subjects having observed QTcF above 480 msec or change from baseline above 30 msec in any of the treatment groups.

4.4.2 HR

There were no subjects having observed maximum HR above 100 beats/min or minimum HR below 45 beats/min in any of the treatment groups.

4.4.3 PR

None of the subjects experienced PR >220 msec and 25% increase over baseline in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

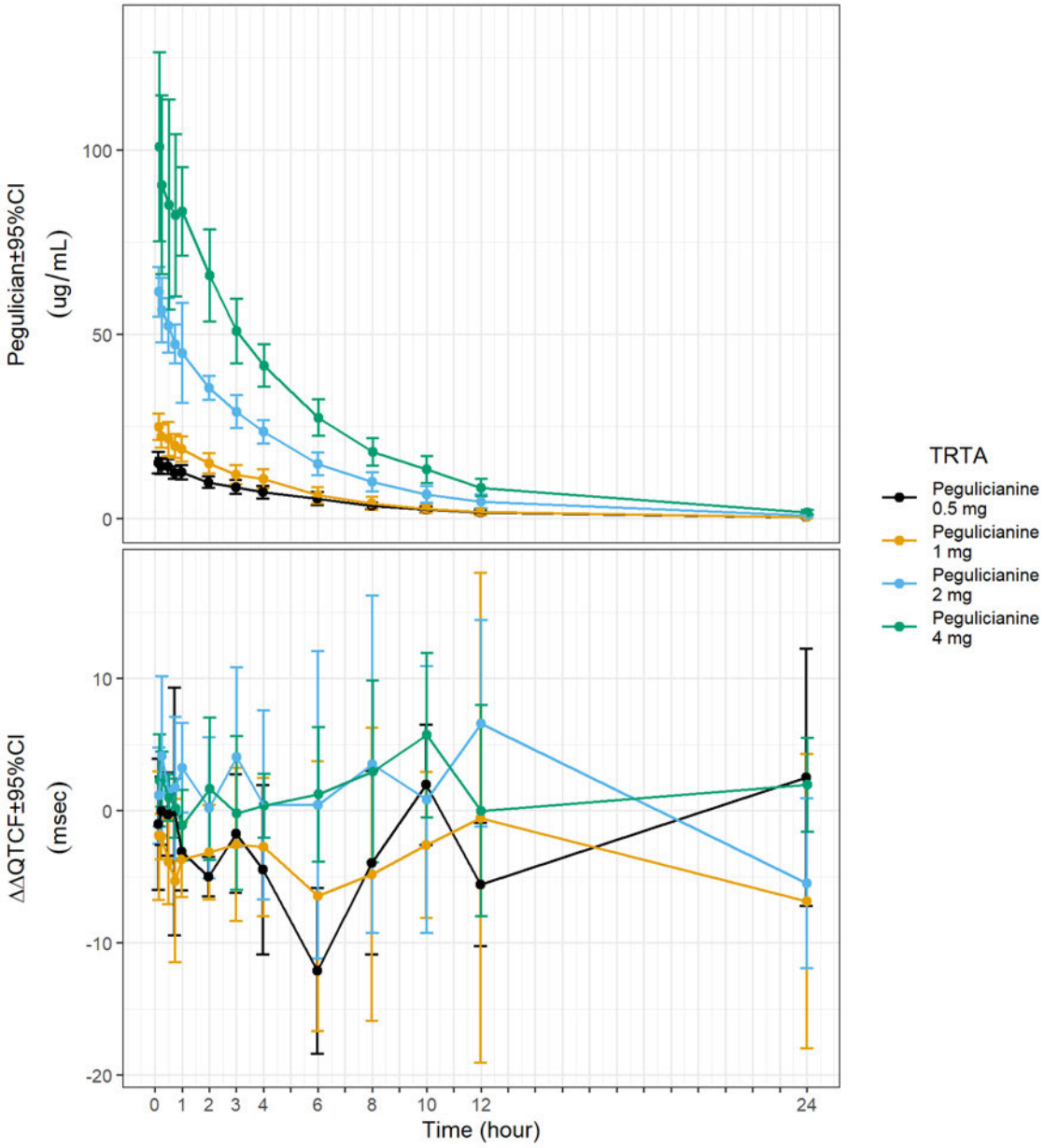
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

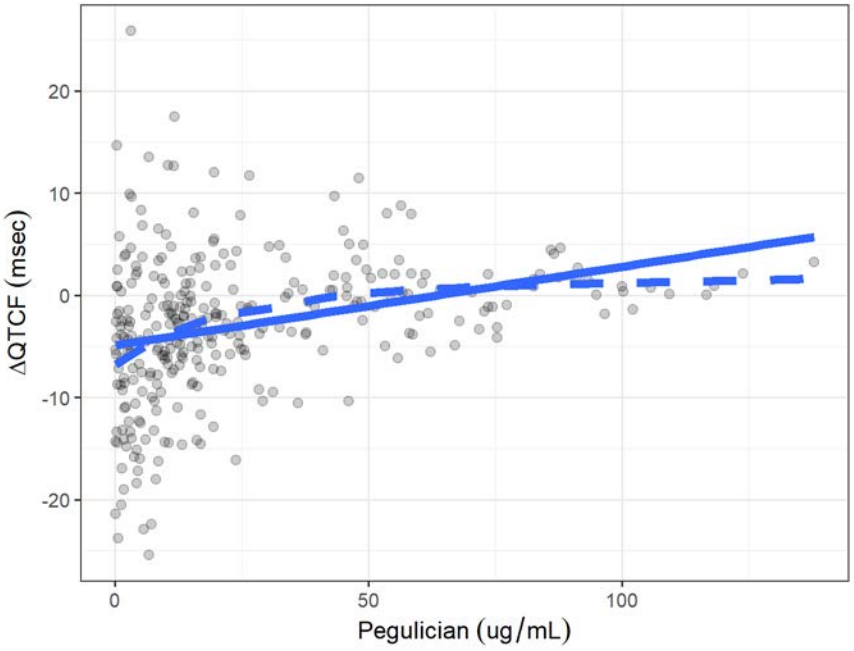
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 3.

Figure 7: Goodness-of-fit Plot for QTcF

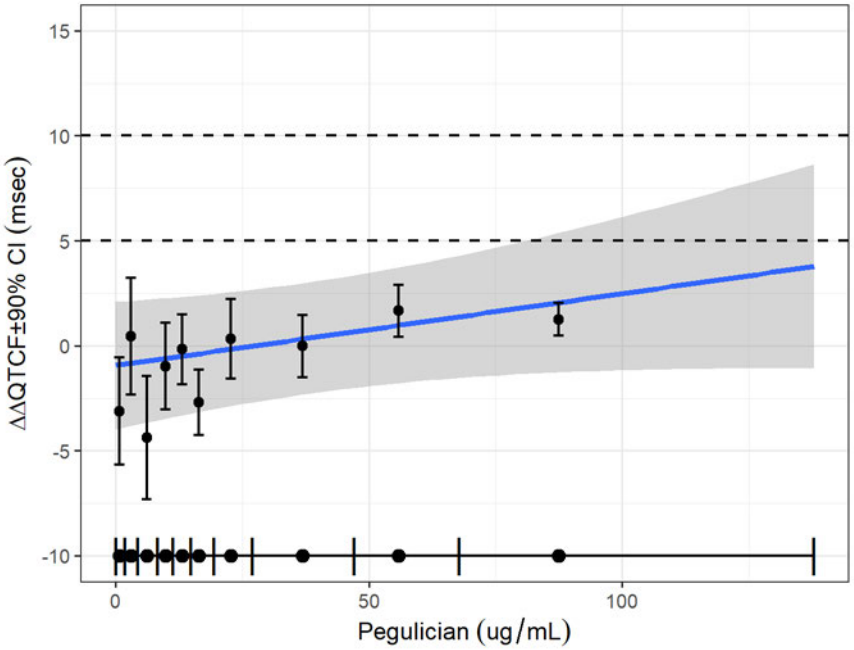


Table 3: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Pegulicianine (ug/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Pegulicianine 0.5 mg/kg	1	15.2	-0.4	(-3.2 to 2.4)
Pegulicianine 1 mg/kg	1	24.8	-0.1	(-2.8 to 2.6)
Pegulicianine two 1 mg/kg injections with 6 hours interval		36.3	0.3	(-2.4 to 3.0)
Pegulicianine 2 mg/kg	1	63.3	1.2	(-1.6 to 4.1)
Pegulicianine 4 mg/kg	1	99.5	2.5	(-1.2 to 6.1)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted

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