CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214511Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND111670

MEETING MINUTES

Lumicell, Inc.
Attention: Jorge Ferrer, PhD
Senior Vice-President, Clinical Research and Strategy
275 Washington Street
Suite 200
Newton, MA 02458

Dear Dr. Ferrer:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LUM015/LUMISIGHT.

We also refer to the videoconference between representatives of your firm and the FDA on May 20, 2022. The purpose of the meeting was to discuss the results from a clinical trial prior to PMA submission and completion of rolling NDA submission.

A copy of the official minutes of the meeting/videoconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Imaging and Radiation Medicine
Division of Regulatory Operations- Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 20, 2022; 12 pm – 1pm ET
Meeting Location:	Videoconference
Application Number:	IND 111670
Product Name:	LUM015/LUMISIGHT
Indication:	LUM015 is an activated fluorescent imaging agent for intraoperative use in breast cancer patients to locate residual abnormal tissue during breast cancer surgery
Sponsor Name:	Lumicell, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Libero Marzella, MD, PhD
Meeting Recorder:	Alberta Davis-Warren

FDA ATTENDEES

Charles Ganley, MD, Director, OSM, CDER
Libero Marzella, MD, PhD, Director, DIRM, CDER
A. Alex Hofling, MD, PhD, Deputy Director, DIRM, CDER
Shane Masters, MD, PhD, Clinical Team Leader, DIRM, CDER
Stephanie Coquia, MD, Medical Officer, DIRM, CDER
Jonathan Cohen, PhD, Pharmacologist, DPT-ORPURM/SM, CDER
Sunny Awe, PhD, Pharmacology, Toxicology Reviewer, DPT-ORPURM/SM, CDER
Sue-Jane Wang, PhD, Deputy Director, DBI, CDER
Sungwon Lee, PhD, Primary Statistical Reviewer, DBI, CDER
Christy John, PhD, Clinical Pharmacology Team Leader, DCPI, CDER
Edwin Chow, PhD, Clinical Pharmacology Reviewer, DCPII, CDER
Devin Kane, PharmD, Safety Evaluator, DMEPA, OSE, CDER
Kyong Kaye Kang, PharmD, Chief Project Manager, DIRM, DROSM, CDER
Colin Kejing Chen, PhD, Team Leader, DHT4A, CDRH
Steven Nagel, MD, Medical Officer, DHT4A, CDRH
James Bertram, PhD, CDRH
Alberta Davis-Warren, RPM, DIRM, DROSM, CDER

SPONSOR ATTENDEES

Jorge Ferrer, PhD, Lumicell, Senior Vice President, Clinical Research and Strategy
Kevin Hershberger, Lumicell, Chief Executive Officer
Michael Viscido, Lumicell, Vice President, Quality
Dan Harris, PhD, Lumicell, Vice President, Pharmaceutical Development and CMC
Sean Madden, PhD, Lumicell, Senior Vice President, Research and Development
Manna Chang, PhD, Lumicell, Principal Data Scientist
Kate Smith, MPH, CCRP, Lumicell, Senior Director, Clinical Affairs
Brian Schlossberg, PhD, Lumicell, Senior Director, Medical Affairs

(b) (4)

1.0 BACKGROUND

LUMISIGHT is the drug constituent of the combination product Lumicell Direct Visualization System. On March 28, 2018, CDRH granted Breakthrough Device designation for the proposed use in patients undergoing a breast conserving surgery to remove breast cancer. DIRM granted fast track designation for intraoperative use in breast cancer patients to locate residual abnormal tissue during breast cancer surgery on October 29, 2020. DIRM also granted the request for rolling review of the NDA. DIRM has received two out of the three parts of the NDA submission. The first portion was submitted to DIRM on July 15, 2021, and the second portion on November 11, 2021. The sponsor will also submit a PMA to CDRH.

On March 9, 2022, Lumicell submitted a meeting request to DIRM. The purpose for the meeting is to discuss the results from the clinical trial under IDE G140195 and how to submit the results in the upcoming PMA submission and to the final portion of the sponsor's NDA rolling review submission.

FDA sent Preliminary Comments to Lumicell on May 18, 2022.

2.0 DISCUSSION

The sponsor's slide presentation assisted in the meeting discussion. The discussion focused on Additional Clinical Comment 1A, the upcoming final portion of the NDA rolling review submission, and the PMA submission.

1. Does the Agency agree that the efficacy data from the clinical development program in breast cancer for the Lumicell DVS appear reasonable to support the

submission of a traditional PMA and the submission of the final portion of the rolling NDA for this combination Breakthrough Device and Fast Track drug product?

FDA response to question 1:

You have provided efficacy data from the pivotal study of the Lumicell DVS for assisting intraoperative detection of residual cancer in the tumor bed of female patients with breast cancer after excising the main lumpectomy specimen, in order to visualize cancerous tissue remaining in the cavity. While the efficacy data from the Lumicell DVS clinical development program appear reasonable to support the submission of the final portion of the rolling NDA to CDER and the PMA to CDRH, the adequacy of the submitted data to meet evidentiary standards for effectiveness will be a review issue.

2. Does the Agency agree that the safety data for the Lumicell DVS appear reasonable to support the submission of a traditional PMA and the submission of the final portion of the rolling NDA for this combination Breakthrough Device and Fast Track drug product?

FDA response to question 2:

We agree that the preliminary safety data submitted for the Lumicell DVS appear reasonable to support the submission of the final portion of the rolling NDA. Please confirm the timing of when the patient-reported outcome data will be submitted to the NDA relative to the timing of the final submission. Based on the meeting minutes for (b) (4) **it is our understanding you will submit the information in an amendment to the NDA within 4 months after submission of the final portion of the NDA.**

ADDITIONAL COMMENTS

Clinical

1. **In your marketing applications, please address the following:**
    a. **In Table 5 of your meeting package, you state that**
        - **nine patients with SOC positive margins coverted to negative margins and**

- **twenty-seven patients had residual cancer removed in a Lumicell DVS-guided shave after the SOC procedure was completed, and**
- **only one patient overlapped in the above two groups.**
  We are unclear why there was only one common patient between both groups. Please provide additional information on how conversion to negative margins was achieved without residual cancer being removed in a Lumicell DVS-guided shave for the other eight patients with SOC positive margins.

Meeting Discussion: The sponsor explained in greater detail the use of the Lumicell DVS after the SOC procedure. The sponsor also stated that the reason why the other eight patients converted to negative margins was that the additional tissue removed in a Lumicell DVS-guided shave created sufficient distance from the primary tumor to result in final negative margins, despite the shave itself containing no cancer (false positive). The sponsor will address this in more detail in the NDA and PMA submssions.

The Division acknowledged the information presented at the meeting and noted that this will be a review issue for the NDA.

b. **In Table 11-23: Summary of Therapeutic Shaves by Type of SOC Procedure (mITT population), our expectation would be that the proportion of patients having at least one therapeutic shave would have been less in the SOC comprehensive shave group than in the SOC selective shave group, but the proportions appear similar. Please comment.**
c. **For the patient-reported outcome data, please present results according to whether therapeutic shaves were taken and by number of shaves taken.**
d. **We note the Table 4 results for endpoints f, g, and h (incremental volume of tissue removed from Lumicell DVS-guided shaves, contribution of Lumicell DVS-guided shaves to total volume of resections, and number of Lumicell DVS-guided shaves taken per patient). Please provide the results for similar analyses among only those patients who had at least one therapuetic shave removed.**
e. **We note the differences in the pivotal study and Phase C Feasibility study results for tissue-level sensitivity and specificity and rate of removal of cancer. Please comment on why differences may exist.**

2. **We remind you of our previous communications under IDE, Q-submission, IND, and pre-NDA that commented on how the efficacy, safety, and study conduct data should be presented in the marketing applications.**
    a. **We request that you provide narratives and case report forms for all patients who experienced SAEs, AEs that resulted in discontinuation of LUMISIGHT, or AEs that required lab draws for suspected allergic reactions, regardless of attribution to the drug or whether the injection was completed.**
    b. **Provide as much detail as possible for all observed protocol deviations, including when they occurred relative to completion of SOC procedures and the reasoning for such protocol deviations or instances of non-compliance (see comments for IDE G140195/R018, IDE G140195/S045, IDE G140195/R017, and IDE G140195/S039).**
    c. **Include the proportion of patients who had residual tumor indicated by Lumicell DVS but who were unable to have a therapeutic shave removed due to reaching the two-shaves per orientation maximum. Provide the total number of indicated shaves that could not be removed due to the two-therapeutic shaves per orientation maximum (see comment for IDE G140195/S039).**

Clinical Pharmacology

In the planned NDA submission, the clinical pharmacology package should include the following:

1. **Address the following questions in the Summary of Clinical Pharmacology:**
    a) **What is the basis for selecting the dose and dosing regimen used in the trials intended to support your marketing application?**
    b) **What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?**
        i. **Provide data that showed LUM015 is not metabolized by hepatic enzymes.**
        ii. **Provide data that showed the major elimination route of LUM015.**
    c) **How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure or safety?**
    d) **How is the optimal imaging window determined? Provide available imaging data from different imaging intervals in all clinical trials and data to support that 4 hours post-injection is the optimal imaging window**
    e) **What is the effect of LUM015 on the QT/QTc interval?**

2. **Apply the following advice in preparing the clinical pharmacology sections of the original submission:**

    a) **Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**

        i. **Particularly, provide data and chromatogram that showed LUM015 remained intact after 4 hours in plasma.**

    b) **Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.**

    c) **Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The individual subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.**

        i. **Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

Discussion of Sponsor's plans to submit final portion of NDA submission and PMA: The Sponsor proposed submitting the final portion of the NDA July-August 2022 and the PMA August-September 2022. CDRH stated that submitting the applications closer together makes it easier for the two teams to work together. CDRH also noted that if both submissions lead to positive decisions, they would need to coincide. The Sponsor will keep the Agency informed regarding the timelines.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

On December 16, 2020, the Division of Imaging and Radiation Medicine issued an Agreed Initial Pediatric Study Plan Agreement letter to the sponsor.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable,

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[4]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slide presentation

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[4] https://www.fda.gov/media/85061/download

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/

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IND111670

MEETING MINUTES

Lumicell, Inc.
Attention: Jorge Ferrer, Ph.D.
Senior Vice-President, Clinical Research and Strategy
275 Washington Street
Suite 200
Newton, MA 02458

Dear Dr. Ferrer:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LUM015.

We also refer to the telecon between representatives of your firm and the FDA on December 16, 2020. The purpose of the meeting was to discuss the CMC development program and cardiovascular safety data collected to date.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Imaging and Radiation Medicine
Division of Regulatory Operations – Specialty Medicine
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 16, 2020; 4:00 pm-5:00 pm ET
Meeting Location: Teleconference

Application Number: IND 111670
Product Name: LUM015

Indication: (b) (4)

Sponsor Name: Lumicell, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Libero Marzella, MD, PhD
Meeting Recorder: Alberta Davis-Warren

FDA ATTENDEES

Charles Ganley, MD, Director, OSM
Libero Marzella, MD, PhD, Director, DIRM
Alex Gorovets, MD, Deputy Director, DIRM
August Hofling, MD, PhD, Clinical Team Leader, DIRM
Stephanie Coquia, MD, Clinical Reviewer, DIRM
Joseph Rajendran, MD, Clinical Reviewer, DIRM
Calvin Han, MD, Clinical Reviewer, DIRM
Jian Wang, PhD, Clinical Analyst, OSM
Sunny Awe, PhD, Pharmacology/Toxicology Reviewer, DPTRDPURM
Brian Booth, PhD, Director, DCPI
Edwin Chow, PhD, Clinical Pharmacology Reviewer, DCPII
Danae Christodoulou, PhD, Branch Chief, OPQ, DNDPIII
Eldon Leutzinger, PhD, CMC Team Leader, OPQ, DNDPIII
Christopher Galliford, PhD, CMC Reviewer, OPQ, DNDPIII
Sue-Jane Wang, PhD, Deputy Director, DBI
Jyoti Zalkikar, PhD, Secondary Statistical Reviewer, DBI
Sungwon Lee, PhD, Primary Statistical Reviewer, DBI
Shannon Heine, PhD, Microbiology Reviewer, DMAII
Devin Kane, PharmD, DMEPA reviewer, OSE
Neil Ogden (CDRH)
Kejing Chen (CDRH)

Alberta Davis-Warren, RPM, DIRM, DRO-SM

SPONSOR ATTENDEES
Jorge Ferrer, PhD, SVP, Clinical Research and Strategy, Lumicell
Dan Harris, PhD, VP, Pharmaceutical Development and CMC, Lumicell
Kate Smith, Senior Director, Clinical Affairs, Lumicell
Kevin Hershberger, Chief Executive Officer, Lumicell
(b) (4)

1.0 BACKGROUND

On October 20, 2020, Lumicell submitted a meeting request to the Division of Imaging and Radiation Medicine. The purpose for the meeting is to receive feedback on key CMC issues prior to NDA submission and comments regarding the cardiovascular safety data as requested in the meeting minutes for the Type C meeting held on July 29th, 2020. As stated in the meeting package, the LUM015 for Injection drug product is the imaging agent component of the LUM Imaging System, an intraoperative medical imaging device combination product. (b) (4)

The meeting was granted on November 6, 2020 to occur on December 16, 2020.

FDA sent Preliminary Comments to Lumicell on December 9, 2020.

2.0 DISCUSSION

The sponsor provided their meeting minutes on January 7, 2021. Their comments are incorporated in the meeting minutes.

CMC:

Drug Substance

1a. Are the justifications for starting material selection and proposed starting material specifications sufficient to support the NDA submission?

FDA response to question 1a:

The starting material proposals appear adequate.

The sponsor accepted FDA's response, no discussion occurred.

1b. For the starting material [redacted] Are summaries of the analytical methods and manufacturing process, along with summaries of the results of validation activities (process validation reports, method validation reports) sufficient to support the NDA submission?

FDA response to question 1b:

The [redacted] information appears adequate.

The sponsor accepted FDA's response, no discussion occurred.

2. LUM015 drug substance has been characterized for physical, chemical properties and structural assignment. [redacted] Does the FDA agree with the testing regiment for [redacted] LUM015 acetate and the additional characterization and structural verification [redacted] as suitable for an NDA?

FDA response to question 2:

Testing regiments for [redacted] API appear adequate.

The sponsor accepted FDA's response, no discussion occurred.

3. Does the Agency agree with the proposed impurity identification, classification, and qualification? Specifically regarding:
   a. Acceptability of our identified and characterized process impurities
   b. Acceptability of our identification and characterization of degradation impurities

FDA response to question 3:

Impurity identification and characterization appear adequate; however, final impurity limits will be assessed during NDA review.

The sponsor accepted FDA's response, no discussion occurred.

4. Does the FDA agree to the proposal to drop the functional assay as a release test?

FDA response to question 4:

Yes, we agree with this proposal.

The sponsor accepted FDA's response, no discussion occurred.

Drug Product

5. An initial commercial batch size for the manufacture of LUM015 for Injection of (b) (4) is proposed for the NDA and the process is planned to be validated prospectively by performing three process validation batches at (b) (4) Information supporting the validation of the sterility assurance will be incorporated by reference to the contract manufacturer's DMF.

   Validation of (b) (4) Does the Agency agree with this validation strategy?

   FDA response to question 5:

   The information provided supporting the validation of the sterility assurance appears reasonable; however, the study methods and validation data will be reviewed upon submission of the NDA. It is acceptable that validation of (b) (4)

   The sponsor accepted FDA's response, no discussion occurred.

6. Does the FDA agree that, for the drug product, the analytical tests and controls included in the specification are adequate for the NDA?

   FDA response to question 6:

   With the modifications that follow below, the release specifications appear to be acceptable.

   Your HPLC identity test should specify a quantitative relative retention time (RRT) from the injected sample to the reference standard. The retention times of each should be recorded in the batch record. In general, acceptance criteria should be quantitative where possible and statements such as (b) (4) should be avoided.

   You should provide justification for NMT than (b) (4) % level of the impurity at (b) (4) Clarify whether this impurity has been isolated and identified.

   The release criterion for reconstitution time appears to be unnecessarily (b) (4) The recorded data for batches B18090069, B180080077, B18090081 and B19070077 are all (b) (4) In particular,

the process validation batch B19070077 underwent reconstitution in (b) (4) seconds. Therefore, in order to make this a meaningful quality test, we recommend (b) (4) the release specification.

In a similar vein to the recommendation above, the observed data for the Karl Fischer test do not exceed (b) (4) %. Therefore, your proposed limit of (b) (4) % seems rather high to be useful as a quality test.

The microbiology tests and controls included in the specification appear reasonable; however, the final decision regarding these specifications will be determined once the NDA application has been received and reviewed by the Agency. Note, the test method (compendial or in-house) to be used should be included in the table provided.

The sponsor accepted FDA's response, no discussion occurred.

7. Lumicell has performed Leachables and Extractables studies in alignment with the thinking publicized by Product Quality Research Institute (PQRI) and USP <1663> and <1664>. The results did not identify any leachables components that present a safety concern and no impurity/matrix specific method validations or long-term studies are planned. Does the Agency agree with this approach?

FDA response to question 7:

The leachables and extractables study appears to be adequate. The results of this study will be reviewed in detail at the time of NDA submission.

In addition, we recommend a full photostability study per ICH Q1B be performed to ensure that no degradants resulting from your dye arise from prolonged storage.

The sponsor accepted FDA's response, no discussion occurred.

8. Primary stability data is being generated on drug product manufactured at our commercial manufacturer, (b) (4), with supportive data provided on the last 3 clinical lots manufactured at (b) (4) During development, (b) (4) Would the Agency like to review the format and content for the SAS transport files prior to inclusion in the NDA submission?

FDA response to question 8:

You should provide a comprehensive set of stability data that includes data under standard and accelerated conditions for review at the time your NDA is submitted. The available data for both sets of storage data will be compared and a conclusion made at that time. A lack of sufficient primary stability data to support the new temperature may result in a significantly shortened shelf-life. You may perform cycling temperature studies for your product per ICH Q1A. Alternatively, a post approval supplement with adequate stability data may provide a pathway to modify the storage conditions.

The sponsor accepted FDA's response, no discussion occurred.

Clinical/Clinical Pharmacology:

9. Is the information provided regarding the cardiovascular safety sufficient to support the submission? If not, could the Agency provide guidance as to what additional information might be required?

FDA response to question 9:

The proposed QT assessment may not be adequate to assess the effect of LUM015 on the QTc interval since there is no concentration-QT assessment in the meeting package. We recommend that you collect PK and ECG data in ongoing trial(s) in a subset of patients receiving the highest proposed recommended diagnostic dose of LUM015 to further assess QT. Intense ECG and PK matched sample collection around T_{max} of LUM15 and Fragment 3 (e.g., pre-dose, end of injection, 10 and 45 min, and 3, 6, 24 hours post-dose) are recommended in this patient subset.

Prior to revising any protocols, we recommend that you submit to the IND a QT assessment plan (including a detailed statistical analysis plan) for FDA to review. Refer to the following FDA document for greater details: "E14 Clinical Evaluation of QT/QTc" <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0>. In general, alternative QT study designs are acceptable for drugs where a thorough QT/QTc study is not feasible or ethical (see ICH E14 Q&A 6.1). These alternative QT studies are usually designed to exclude large mean increases in QTc (e.g., >20 ms). When submitting the QT assessment plan, please include the following together with the clinical study protocol(s):

a) **Statistical analysis plan. The statistical analysis plan for QT assessment should include a description of the primary (i.e., by-timepoint analysis or concentration-QTc analysis) and secondary analyses as well as a justification of the sample size.**
b) **Investigator's Brochure**

c) A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (https://www.fda.gov/media/129685/download)
Following our review of your QT assessment plan, we may provide additional guidance on how to revise your protocol(s) to collect the necessary PK and ECG data in an appropriate number of patients.

Additionally, we have the following comments for you to consider:

1. **For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).**
2. **If there is a need to pool data from multiple studies to cover a wide range of doses/exposures or to increase the number of subjects exposed to the drug at higher doses, it is important that similar clinical conduct and subject handling are present in each study and that the ECG acquisition and ECG measurement approaches as well as the bioanalytical assay are similar. You should test for heterogeneity before pooling data from multiple studies. If one study has appropriate sample size and ECG/PK sampling, that study could be used as a pivotal study for analysis and pooled data used as supportive analysis.**

Meeting Discussion:

The sponsor provided their slide presentation that assisted in the discussion.

The sponsor began the discussion stating the CMC responses adequately addressed their questions; the sponsor wanted to discuss the cardiovascular safety information and their plans for the NDA submission.

FDA confirmed that their recommendations were informed by Appendix 9 (provided in the briefing package). FDA commented that the data therein were very limited to assess cardiovascular safety.

FDA discussed subjects to be studied. FDA indicated that from a clinical pharmacology perspective, it is preferred that the study be done in healthy volunteers. The sponsor discussed that they would like to consider both options (healthy volunteer study vs. adding to ongoing study) for now. The sponsor inquired that if a feasible option existed to conduct the study in ongoing trials that alleviated some patient-specific issues, would FDA be open to that option. FDA indicated they would be open to either option. FDA further specified that, if done in patients, there was not a preference for the type of patient or cancer, so long as the dosage(s) cover the maximum exposure. With regard to a patient

study, the sponsor inquired if variable timepoints would be acceptable. FDA responded that they would need to review the proposed justification if provided in an amendment to an ongoing protocol to determine the acceptability of the justification. FDA inquired about the doses to be studied. Lumicell indicated that up to three doses may be studied if the trial is conducted in healthy volunteers.

> **POST MEETING COMMENT: We note that doses higher than the proposed 1 mg/kg dose for breast cancer are being evaluated in other populations. Note that if the QT study maximum dose is 1 mg/kg, it would not be able to support any future supplemental NDAs recommending doses higher than 1 mg/kg. This should be taken into account when deciding which doses to evaluate and whether to make the QT study as part of a specific ongoing study.**

The sponsor inquired if the QT study (b) (4) **FDA indicated the study must be complete before approval. FDA also stated Fast Track Designation does not apply to safety. Lumicell inquired if submission of the QT study report could occur after Module 5 submission. FDA stated that the study report should be submitted with the other Module 5 documents. The Agency stated that it would use its best efforts to expedite review of Module 5 when submitted.**

The sponsor proposed that if the study is done in patients, the protocol amendment will be submitted to the IDE. Alternatively, if done in healthy volunteers, the protocol will be submitted to the IND. FDA agreed with this approach as the protocol would be reviewed wherever submitted.

The sponsor proposed a (b) (4) **in lieu of a thorough QT study. FDA replied that the proposal appeared reasonable, however, adequate justification and proper powering of the selected sample size would be required. FDA indicated they would review the study design in advance of study initiation.**

The sponsor also presented their updated plan for rolling submission of the LUM015 NDA. FDA did not have any comments regarding the sponsor's proposed plan. The sponsor also inquired about additional information needed to make a determination of the need for a REMS. FDA replied that no additional information was required at this time. The need for a REMS will be discussed further during the NDA review cycle.

3.0 Additional Comments

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 6, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via

[5] http://www.fda.gov/ectd

the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[7]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				

[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[7] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials).

[8] https://www.fda.gov/media/84223/download

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's slide presentation

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

[10] https://www.fda.gov/media/85061/download

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/

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