CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216203Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135095

MEETING REQUEST-
WRITTEN RESPONSES

Lexicon Pharmaceuticals, Inc.
Attention: Ken Kassler-Taub, MD
Vice President, Regulatory Affairs
110 Allen Road
Basking Ridge, NJ 07920

Dear Dr. Kassler-Taub:

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

We also refer to your submission dated May 20, 2021, containing a meeting request. The purpose of the requested meeting was to discuss the proposed questions that will inform an NDA submission for the indication proposed.

Further reference is made to our Meeting Granted letter dated May 24, 2021, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 18, 2021 background package.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Enclosure: Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Pre-NDA
Meeting Category: B

Application Number: 135095

Product Name: sotagliflozin
Indication: To reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, (b) (4) (b) (4) in adults with type 2 diabetes mellitus and chronic kidney disease with other cardiovascular risk factors, including those with a history of heart failure (b) (4)

To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction

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

1.0 BACKGROUND

Sotagliflozin is a sodium-glucose co-transporter type 1 (SGLT1) and sodium-glucose co-transporter type 2 (SGLT2) inhibitor currently under investigation for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) under IND 102191 and for heart failure under IND 135095. Sotagliflozin received marketing authorization in 2019 in Europe as an adjunct to insulin to improve glycemic control in patients with T1DM and body mass index (BMI) >27. A complete response letter was issued in 2019 by Division of Metabolism and Endocrinology for an NDA in T1DM. Two large CV outcome trials were being conducted: 1) patients with T2DM and with chronic kidney disease (CKD) (SCORED; under the IND 102191 and 2) patients with T2DM with worsening HF (SOLOIST; under an IND 135095). The Sponsor submitted a meeting request in December 2019 asking for feedback on changes to study population, study endpoints and sample size in SOLOIST. In a Written Response, DCN found the proposed changes acceptable.

Both trials were terminated in March 2020 for business reasons as well as operational challenges associated with COVD-19. The proposed trial modifications were never instituted. Although the trials had not reached intended enrollment or duration of follow up, in consultation with Steering Committees for the studies, it was decided to conduct a formal analysis on key endpoints. The Sponsor is not seeking a specific indication in

T2DM, but, based on the results of the 2 trials, the Sponsor is proposing to submit an NDA to the Division of Cardiology and Nephrology. A meeting request was submitted to discuss the proposal but was subsequently cancelled after review of FDA's preliminary comments dated January 6, 2021.

This meeting request is the pre-NDA meeting to discuss format and content in preparation for the NDA submission.

2.0 QUESTIONS AND RESPONSES

1. The Sponsor's proposed primary analysis approach and plans to address the Agency's requested analyses of the SCORED and SOLOIST studies communicated in their January 2021 Type C Meeting Preliminary Comments (Reference ID: 4727264) are described in the Sponsor Position [on pages 14-16 of the briefing package (BP)]. Can the Agency comment on this proposed analysis plan?

   FDA response:

   a. You proposed a marginal Cox proportional hazards (PH) model as the primary efficacy analysis method for the possible recurrent time-to-event endpoint. Please provide details on the specific model that you will use. You also treat the non-CV deaths as competing events. Please clarify how you plan to include non-CV deaths as competing events in your marginal Cox PH model. One way we accept is to treat the non-CV death as non-informative censoring and propose competing risk models for non-CV deaths as sensitivity analyses.

   b. Given intercurrent events such as patient hospitalization caused by COVID-19 and censoring caused by operational challenges associated with COVD-19, please propose a proper estimand and a detailed description on how to handle such intercurrent events.

   c. For both trials, you propose to analyze the rate of decline in eGFR over time using a repeated measures mixed-effects model with absolute change in eGFR from baseline to the end of the study as the outcome, a random effect for intercept, and fixed effects for treatment, baseline value, and time; however, it does not appear that the proposed eGFR analysis was pre-specified for either trial. As we understand, the pre-specified renal endpoint for both trials was a composite of a sustained ≥50% decrease in eGFR from baseline, chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2. After early termination of the trials but before database lock, SAPs were developed and finalized, and the amended SAP for the SOLOIST trial added a new secondary endpoint of "rate of decline in eGFR after Week 4… to the end of the study" to the testing hierarchy. As we understand from the materials for our January 2021

meeting, none of the three secondary renal endpoints reached statistical significance (b) (4).

2. Regarding pooled analyses and the integrated summaries of safety and efficacy:
   a. The Sponsor's proposed primary approach to address the Agency's request for 3 combined integrated efficacy analyses communicated in their January 2021 Type C Meeting Preliminary Comments (Reference ID: 4727264) are described in the Sponsor Position [on pages 16-17 of the BP]. Can the Agency comment on the proposed analysis plan?

      FDA response:
      Per FDA request (dated January 2021), you propose to provide the following additional pooled analyses from the SCORED and SOLOIST studies:

      - A figure displaying treatment effect (hazard ratio) for the Investigator-reported primary efficacy endpoint by left ventricular ejection fraction at Screening in patients with a history of heart failure,
      - A time-to-event analysis of a composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, and
      - Analysis of total occurrence of cardiovascular death, non-fatal infarction, and nonfatal stroke.

      Your proposal is reasonable.

   b. Given the differences in enrolled populations between the SCORED and SOLOIST studies, the Sponsor does not believe that an integrated analysis of safety combining data across these populations will meaningfully inform the review of the HF NDA. However, side-by-side tabular summaries of key safety data will be generated and included in Module 5, Section 5.3.5.3, and discussed in Section 2.7.4 of the NDA. Can the Agency comment on their views regarding this approach?

      FDA response:
      The proposed approach seems reasonable.

   c. Does the Agency agree with the placement of textual summaries of the integrated analyses of safety and efficacy (ie, the summaries that would normally be included in the integrated summary of efficacy [ISE] and integrated summary of safety [ISS]) within Module 2 as part of Sections 2.7.3 and 2.7.4, respectively, and placement of any statistical outputs of integrated analyses or other summaries of data from both SCORED and SOLOIST in Module 5, Section 5.3.5.3?

      FDA response:
      Yes

3. Lexicon's proposal for popPK and E-R analyses are described in the Sponsor's Position [on pages 21-25 of the BP]. Can the Agency provide their feedback on the proposed plan?

   FDA response:
   Your proposed plan to conduct population PK analysis and exposure-response analysis for select safety assessments seems reasonable. Since you plan to pool data from several studies for the planned population PK analysis, we recommend you also include a by-study tabulated summary of bioanalytical method performance for the trials, including analytical range, LLOQ, precision and accuracy, duration between sample collection and analysis.

   Please confirm if the SCORED and SOLOIST studies utilized the intended commercial formulation of sotagliflozin.

4. Does the Agency agree that the information submitted in the T1D NDA 210934 will be adequate for the [drug abuse liability assessment] DALA?

   FDA response:
   Yes, we agree.

5. Lexicon plans to communicate potential risks of the use of sotagliflozin in the Warnings and Precautions Section of the proposed product labeling and in a Medication Guide. Given that the Agency has not reviewed the primary data yet, does the Agency anticipate the need for a formal Risk Evaluation and Mitigation Strategy (REMS) for this indication?

   FDA response:
   At this time and based on the information currently available, we do not believe that a REMS will be necessary.

6. Sotagliflozin has been demonstrated to reduce CV death, HHF, or urgent HF visits in the SCORED and SOLOIST trials in two at-risk patient populations with significant unmet need: T2D patients with CKD and other CV risk factors such as HF including HF either with reduced or preserved ejection fraction (HFrEF or HFpEF, respectively); and T2D patients who are hospitalized with acute decompensation of HF. Can the Agency comment on Lexicon's proposed rationale, as described in the Sponsor Position [on pages 27 through 28 of the BP], for the sotagliflozin HF NDA to receive a priority review designation?

   FDA response:

   Given that the intended population includes patients with heart failure with LVEF $\geq$ 50%, a serious condition with no approved treatment, the sotagliflozin NDA will likely be given a priority review designation.

7. Does the Agency have any comments regarding the dossier content, structure, format and electronic table of contents (eTOC)?

   FDA response:
   The proposed contents appear reasonable. The integrated safety datasets from the T2D glycemic control program should also be submitted under Module 5.3.5.3.

8. Does the Agency agree with Lexicon's plan to cross-reference the T1D NDA 210934 submission within the HF submission?

   FDA response:
   Yes, we agree.

9. Does the Agency have any comments regarding the Study Data Standardization Plan (SDSP) submitted and do they have comments about the sample dataset?

   FDA response:
   The proposed SDSP and the plan to submit the sample dataset are acceptable.

10. In the 2021 Type C Meeting Preliminary Comments (Reference ID: 4727264), the Agency requested a specific dataset and table including a list of patients for whom narrative summaries, case report forms (CRFs), MedWatch forms, and/or adjudication packages were to be submitted. Lexicon's proposed format and location for these items is provided in the Sponsor Position [on pages 30 through 31 of the BP]. Does the Agency agree with Lexicon's proposed format and location of the proposed table and the location of the dataset?

    FDA response:
    Yes, the dataset and table should be placed in Section 5.3.5.1 with each of the two study reports.

3.0 OTHER IMPORTANT INFORMATION

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.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

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 and Pregnancy and Lactation Labeling Final Rule 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, 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.

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 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.

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.

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, 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)				
(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[1] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[2]. 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.

[1] https://www.fda.gov/media/84223/download
[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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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/

NORMAN L STOCKBRIDGE
07/14/2021 02:44:09 PM

IND 135095

MEETING PRELIMINARY COMMENTS

Lexicon Pharmaceuticals, Inc.
Attention: Ken Kassler-Taub, MD
Vice President, Regulatory Affairs
110 Allen Road
Basking Ridge, NJ 07920

Dear Dr. Kassler-Taub

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sotagliflozin.

We also refer to your October 30, 2020, correspondence requesting a meeting to discuss cardiovascular outcomes studies, EFC15156 (SOLOIST) and EFC14875 (SCORED) and the potential for submission of data to support a heart failure indication. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Alexis Childers, RAC, CQIA
Sr. Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: January 11, 2021, 10:00-11:00 am EST
Meeting Location: Teleconference

Application Number: 135095
Product Name: sotagliflozin
Indication: reduce the risk of Cardiovascular Death, Hospitalization for Heart Failure or Urgent Visits for Heart Failure in adult patients with Type 2 Diabetes with either worsening heart failure or additional risk factors for heart failure

Sponsor Name: Lexicon Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

FDA ATTENDEES (tentative)

** Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Cardiology and Nephrology (DCN)*

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Safety Director
Charu Gandotra, MD, FACC	Clinical Reviewer
Fred Senatore, MD, PhD, FACC	Clinical Team Leader
Kimberly Smith, MD	Clinical Team Leader

** Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology*

Edward Fromm, RPh, RAC	Chief, Project Management Staff
Alexis Childers, RAC, CQIA	Sr. Regulatory Health Project Manager

**Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Manoj Khurana, PhD	Clinical Pharmacology Team Leader
Snehal Samant, PhD	Clinical Pharmacology Reviewer

**Office of Biometrics, Division of Biometrics I*

Jialu Zhang, PhD	Statistical Team Leader
Fanhui Kong, PhD	Statistician

**OCHEN, Division of Diabetes, Lipid Disorders and Obesity*

Mitra Rauschecker, MD	Clinical Team Leader
Andreea Lungu, MD	Clinical Reviewer

SPONSOR ATTENDEES

(b) (4)

Lonnel Coats	CEO
Praveen Tyle	EVP Research and Development
Phil Banks	Executive Director of Biostatistics
Eshetu Tesfaye	Senior Director of Biostatistics
Suman Wason	Vice President for Clinical Development
Kenneth Kassler-Taub, MD	Vice President Regulatory Affairs, Quality, and Safety
Christine Gathers	Regulatory Consultant

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for January 11, 2021 from 10:00-11:00 am EST between Lexicon Pharmaceuticals, Inc. and the Division of Cardiology and Nephrology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Sotagliflozin is a sodium-glucose co-transporter type 1 (SGLT1) and sodium-glucose co-transporter type 2 (SGLT2) inhibitor currently under investigation for type 1 diabetes mellitus (T1DM) (b) (4) under IND 102191, and for heart

failure under IND 135095. Sotagliflozin received marketing authorization in 2019 in Europe as an adjunct to insulin to improve glycemic control in patients with T1DM and body mass index (BMI) >27. A complete response letter was issued in 2019 by Division of Metabolism and Endocrinology for an NDA in T1DM. Two large CV outcome trials were being conducted: 1) patients with T2DM and with chronic kidney disease (CKD) (SCORED; under the IND 102191 and 2) patients with T2DM with worsening HF (SOLOIST; under an IND 135095). The Sponsor submitted a meeting request in December 2019 asking for feedback on changes to study population, study endpoints and sample size in SOLOIST. In a Written Responses, DCN found the proposed changes acceptable.

Both trials were terminated in March 2020 for business reasons as well as operational challenges associated with COVD-19 outbreak. The proposed trial modifications were never instituted. Although the trials had not reached intended enrollment and/or duration of follow up, in consultation with Steering Committees for the studies, it was decided to conduct a formal analysis on key endpoints. The Sponsor is not seeking a specific indication in T2DM, but, based on the results of the 2 trials, the Sponsor is proposing to submit an NDA to the Division of Cardiology and Nephrology and would like to discuss.

2.0 DISCUSSION

1. Lexicon is proposing to seek the following indication based on the statistically significant and highly consistent results for the primary endpoints of both adequate and well-controlled Phase 3 studies SOLOIST and SCORED:

   Sotagliflozin is indicated to reduce the risk of CVD, HHF, and urgent visits for HF in adult patients with T2DM with either worsening HF or additional risk factors for HF.

   Does the FDA agree that an NDA submission to achieve this indication which is based on all occurrences of Investigator-reported events for CVD, HHF, and UVHF are suitably robust to form the basis of an FDA review for the indication, given that these findings, as analyzed according to the final SAP, are:
   - Consistent across key subgroups
   - Comparable to analyses of adjudicated events only and the originally proposed primary endpoint of time to first occurrence of CVD or HHF based on adjudicated and Investigator-reported events?

   FDA response: We agree that results of SOLOIST and SCORED can support NDA submission for the proposed indication.

2. Based on the data available, does the FDA agree that data showing the benefit of sotagliflozin in reducing the risk for the following events could be considered for inclusion in the Clinical Studies section of the label?
   - Hospitalizations for heart failure and urgent visits for heart failure
   - Hospitalizations for heart failure

- Data summarizing treatment effect on first, second, or third and subsequent events
- [redacted] (b) (4)

FDA response: Based on data provided in the meeting package, pending review, the effect of sotagliflozin on hospitalizations for heart failure and urgent visits for heart failure; hospitalizations for heart failure; recurrent heart failure events; and [redacted] (b) (4) may be considered for inclusion in Section 14.

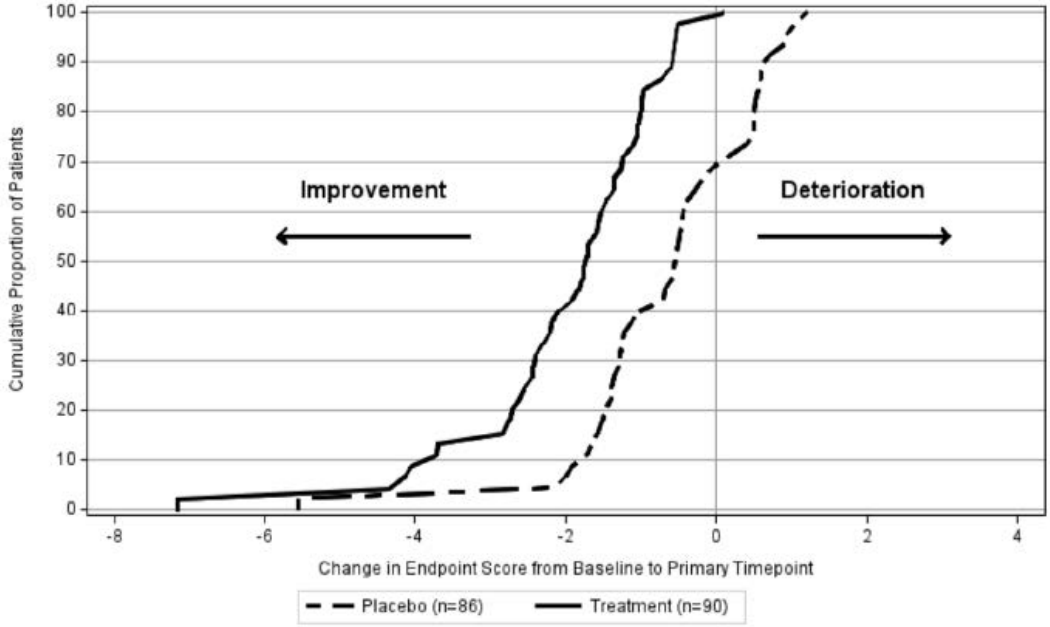
3. Assuming the Agency grants Lexicon the indication as proposed in Question 1, based on the data available, does the FDA agree that [redacted] (b) (4)

   FDA response: [redacted] (b) (4)

4. Lexicon plans to submit data concerning the subgroup analyses identified in the final SAPs for the studies, in addition to the meta-analysis of results from the 2 studies. Are there other analyses that the Sponsor should include as part of the NDA submission?

   FDA response: Consider providing the following analyses as part of the NDA submission:

   1. A graph displaying treatment effect (hazard ratio) for investigator reported primary efficacy endpoint by left ventricular ejection fraction at screening in patients with history of heart failure in SOLOIST and SCORED trials combined.
   2. A time to event analysis of a composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke in SOLOIST and SCORED trials combined.
   3. Analysis of total occurrence of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke in SOLOIST and SCORED trials combined.
   4. KCCQ in SOLOIST
      a. Provide number of patients who completed KCCQ-12 independently versus interviewer-administered.
      b. Clarify if any global assessment of patient's quality of life was conducted to serve as anchor(s) to understand clinical relevance of the observed change in KCCQ.
      c. Provide the variability of KCCQ-12 scores at baseline and Months 4 and 8 for the overall trial population and by treatment arm.
      d. Provide empirical cumulative distribution function (eCDF) of KCCQ-12 raw change scores from baseline to Month 4 and 8 by treatment arms (i.e., sotagliflozin vs. placebo). There should be a curve for each treatment arm. See sample treatment arm eCDF curves below.



5. Is the exposure database from the SCORED and SOLOIST studies, with supporting data from Phase 2 and 3 studies in T2DM and data previously submitted to the FDA in support of an indication in T1DM sufficient for the FDA to use as the basis for determining whether the indication proposed may be approved?

   FDA response: The planned safety database is reasonable to support NDA for the proposed indication.

Additional Requests from the Agency:

1. Please submit the following information at the time of NDA submission:
   a. Protocol and Statistical Analysis Plan (SAP)

      1) All versions of the protocol for SCORED and SOLOIST and the date when changes were implemented. Include a Summary of Changes for each version.

      2) All versions of the SAP for SCORED AND SOLOIST. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

   b. Clinical Trial Materials

   Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as “CRFs” (Medwatch

forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

1) Sample clinical trial kits, from both treatment arms, identical to those used during SCORED AND SOLOIST. Ship them to Alexis Childers' desk address in the same packaging as will be used for shipping to investigative sites.

2) All data management plans for SCORED AND SOLOIST. Cite all amendments for each data management plan, including all manual and programmatical checks.

3) All site monitoring plans for SCORED AND SOLOIST. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

4) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in SCORED AND SOLOIST.

5) All charters for committees involved in conducting SCORED AND SOLOIST (Data Safety Monitoring Board [DSMB], Steering Committee, etc.)

6) All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

7) All newsletters and all other communications to investigational sites and national coordinators from the groups responsible for the conduct of SCORED AND SOLOIST. Please bookmark the communication by date.

c. General Data and Analyses

1) All code and datasets used to create your analyses found in the main sections of your Integrated Summary of Clinical Efficacy, Integrated Summary of Clinical Safety, and Phase 3 trial clinical study reports.

2) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure.

3) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your

datasets are suitable for an NDA review. Submit code that was used to create or clean up your analysis datasets.

4) Kaplan-Meier time to event analysis datasets and code (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Indicate how censoring was determined (e.g., by a patient visit or by telephone call). This dataset should allow one to analyze by intent-to-treat (ITT) as well as on-treatment. The events should include all adjudicated and investigator-reported events, any important composite endpoints, important adverse events, and laboratory parameter changes of interest.

5) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

6) Dataset that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.

7) A table set up similarly to the dataset requested in above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission (subjects with cardiovascular events of interest, subjects with hepatic laboratory anomalies of interest, etc.).

8) One table which includes the following information for SCORED and SOLOIST:
   - Dates of first patient and last patient visits
   - Date of data lock
   - Dates for each interim analysis
   - Dates of all versions of the SAP (with a hyperlink to each SAP)
   - Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

d. <u>Important Endpoints</u>

1) An adjudication dataset for SCORED AND SOLOIST that contains one line per event. The columns in the dataset should include the study number, unique subject id, randomized treatment, actual treatment, flag that indicates subject is included in the ITT analysis, flag that indicates the subject is included in the safety analysis, the event type being adjudicated (i.e., stroke, major bleed, death, hospitalization for heart failure, etc.), date of event, what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the event, each adjudicators' result (in

chronological order across the dataset), date of each adjudication, final adjudication result and date.

2) A comprehensive description of the algorithm used to identify potential endpoint events in your final clinical study report. If your algorithm changed, you should also provide detailed information on its evolution, including when and why changes were made.

3) A summary table displaying number of negatively adjudicated events by endpoint and the reasons for negative adjudication.

Other

1) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

2) Rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS)

There are two major pieces to this applicability of foreign data issue as follows:

- Are the patients the same (US versus rest of the world)?
- Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?

3) An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to 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 reproductive potential.

- Regulations and related guidance documents.

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[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

- 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 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]

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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*.[7]

[7] 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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