CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212839Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76809

MEETING MINUTES

SK Life Science, Inc.
Attention: Darshan Patel
22-10 Route 208 South
Fair Lawn, NJ 07410

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cenobamate (YKP3089).

We also refer to the meeting between representatives of your firm and the FDA on April 4, 2018. The purpose of the meeting was to discuss the appropriate format and content of an NDA for cenobamate.

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

If you have any questions, call LaShawn Dianat, PharmD, Regulatory Project Manager, at (240) 402-7713.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 4, 2018 at 3:00 pm to 4:00 pm (EDT)
Meeting Location:	FDA White Oak Building 22, Conference Room: 1313
Application Number:	IND 76809
Product Name:	Cenobamate (YKP3089)
Indication:	Partial onset seizures
Sponsor Name:	SK Life Science, Inc.
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Susan Daugherty

FDA ATTENDEES

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Philip Sheridan, MD, Clinical Team Leader
Steven Dinsmore, MD, Clinical Reviewer
Kun Jin, PhD, Biometrics Team Leader
Junshan Qui, PhD, Biometrics Reviewer
Jagan Parepally, PhD, Clinical Pharmacology Reviewer
Martha Heimann, PhD, CMC Lead
Stephanie Emory, PhD, Drug Product Reviewer
Ta-Chen Wu, PhD, Acting Biopharmaceutics Team Leader
Banu Zolnik, PhD, Biopharmaceutics Reviewer
Xueli Zhu, PhD, Manufacturing and Process Reviewer
Michelle Mathers, RPM
Susan Daugherty, RPM

SPONSOR ATTENDEES

Jeong Woo Cho, PhD, Chief Executive Officer
Marc Kamin, MD, Chief Medical Officer
Hong Wook Kim, PhD, Chief Operations Officer
Darshan Patel, PharmD, Head, Regulatory Affairs
Sanjana Sheth, MS, RAC, Manager, Regulatory Affairs
Kelli Glenn, PhD, Head, Toxicology
Susan Melnick, PhD, Associate Director, Toxicology
Laurent Vernillet, PhD, PharmD Head, Clinical Pharmacology
Fang Dong, PhD, Head, Biostatistics and Data Management

Mark Friesen, MTM, PMP, Head, Project Management
Augustin Pegan, BS, RPh, Head, Chemistry, Manufacturing and Controls

1.0 BACKGROUND

The purpose of the meeting is to discuss the sponsor's request to discuss the potential submission of an NDA for cenobamate for the treatment of partial onset seizures in adult patients. The product will be reviewed under the Program. No agreements for late submissions were made at the meeting.

2. DISCUSSION

Chemistry, Manufacturing and Controls

Question 1:

Does the Division agree that testing for elemental impurities for cenobamate drug substance is not needed for release testing?

FDA Response to Question 1:

FDA agrees that testing for elemental impurities for cenobamate drug substance is not needed. The risk assessment described in ICH Q3D for elemental impurities in the drug substance has been adequately applied, and it has been demonstrated with appropriate batch analysis data that the risk for elemental impurities through the drug substance manufacturing process is low. We remind you to amend the risk assessment to include the drug product formulation and packaging components and manufacturing process, as described in the guidance, prior to submission of the NDA.

Meeting Discussion

None

Question 2:

Does the Division agree with SKLSI's proposal for providing registration stability data in the NDA for the two new tablet strengths (150 mg and 200 mg)?

FDA Response to Question 2:

We cannot evaluate the acceptability of your proposal based on the information provided in the meeting package. It is not clear how the headspace:drug ratio of the 100 mg tablets on stability compares with that of the 150 mg and 200 mg tablets, or whether the caps and seals are comparable. At or ahead of the meeting, provide a summary of the registration stability packaging configurations for 100 mg, 150 mg, and 200 mg tablets, including bottle count, size, description, and composition, and cap/seal size, description, and composition.

Meeting Discussion

The Sponsor provided the requested information in their handout distributed at the meeting, and the Agency agreed to provide a response in the final meeting minutes.

Post Meeting Comment

After reviewing the additional information, we agree that the sponsor may submit 6 months long-term and accelerated stability data for the 150 mg and 200 mg strength tablets, in addition to the 24 months long-term stability data which will be provided for the 100 mg tablets. However, the expiry date will be a matter for review upon submission of the NDA and will be determined based on the totality of stability data submitted for all tablet strengths.

Question 3:

Does the Division agree to accept executed manufacturing batch record for one registration batch of each tablet strength?

FDA Response to Question 3:

Your proposal to submit executed manufacturing batch record for one registration batch of each tablet strength is acceptable. However, adequacy of the data is a review issue.

Meeting Discussion

None

Question 4:

Does the Division agree that the (b) (4) bottle sizes are bracketed by the existing 30 count (b) (4) bottles?

FDA Response to Question 4:

We agree to the proposed bracketing approach if the bottle seals and caps are the same for all bottle counts (see the information requested in our response to question 2).

Meeting Discussion

In their handout distributed at the meeting, the Sponsor stated, "SKLSI confirms that bottle seals and caps are the same for all bottle counts." There was no further discussion.

Nonclinical

Question 5:

Does the Division agree that the nonclinical package is adequate and complete to support the filing and potential approval of the NDA?

FDA Response to Question 5:

Based on the information provided in the briefing document, it appears that the nonclinical studies to be included in the NDA would be sufficient to support filing; however, the adequacy of the studies to support approval of the NDA will be a matter of review.

Meeting Discussion

None

Question 6:

Does the Division agree that nonclinical study reports which contain amendments will be combined into a single PDF file with appropriate bookmarking to indicate the original report and report amendment(s) in the NDA submission?

FDA Response to Question 6:

We agree.

Meeting Discussion

None

Clinical Pharmacology

Question 7:

Does the Division agree that the Clinical Pharmacology package is adequate and complete to support the filing and potential approval of the cenobamate NDA?

FDA Response to Question 7:

On face, clinical pharmacology studies described in the package to support the cenobamate NDA appear reasonable. Adequacy of these studies would be a review issue.

We note (b) (4)

(b) (4) as defined by the FDA's SUPAC-IR Guidance, for which a bioequivalence (BE) study will be necessary. Please refer to the SUPAC-IR Guidance for the recommended in-vitro and in-vivo BE documentations in support of the formulation bridging.

Meeting Discussion

The Sponsor addressed the FDA preliminary response in their handout distributed at the meeting, suggesting that a BE study is not needed.

(b) (4) As an alternative approach to conducting an in-vivo BE study, the Agency recommended that the Sponsor consider pursuing the BCS Class 1 designation for their proposed drug substance/drug product (which would potentially support a biowaiver) based on the characteristics of solubility, permeability, and dissolution that the Sponsor presented in their meeting handout. For that approach, the Agency can provide a BCS Quest-Based Approach template as guideline, and the Sponsor can submit the request for the BCS classification with all the supporting information/data (refer to FDA's BCS Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf) under an Amendment to the IND. The Sponsor, however, stated that they will consider conducting a BE study. The Agency stated that the BE study report should be included as part of the NDA submission and not submitted later during the NDA review.

Clinical and Statistics

Question 8:

Does the Division agree that the results of Studies YKP3089C013, YKP3089C017 and YKP3089C021 provide substantial evidence of the efficacy and safety and can be the basis of a submission of an NDA for the treatment of patients with partial onset seizures?

FDA Response to Question 8:

The efficacy and safety data from studies YKP3089C013 and YKP3089C017 appear sufficient to support an NDA submission. You have not yet fulfilled the safety objective of study YKP3089C021. In your comprehensive review of cenobamate safety from hypersensitivity report # 18 submitted on February 5, 2018, (SN0257), there were 831 patients reported to have 6 months exposure. We expect that the full cohort of YKP3089C021 study patients (necessary to ensure an upper bound CI of 0.3% DRESS risk) will have completed 6 months exposure at the time of NDA submission.

Meeting Discussion

None

Question 9:

Does the Division agree that Studies YKP3089C013 and YKP3089C017 will not be pooled for efficacy, an Integrated Summary of Efficacy (ISE) will not be provided, and that the Clinical Summary of Efficacy (Module 2.7.3) will be adequate to support the efficacy conclusions?

FDA Response to Question 9:

We are in agreement with your conclusion that studies YKP3089C013 and YKP3089C017 are too divergent in design for formal pooling. This difference in studies should not exclude a integrative discussion that compares the study designs, examines responses across different populations, and provides a comprehensive analysis of effectiveness. This presentation may be placed in the Clinical Summary of Efficacy if this can be accomplished within the space limitations of the Module. However, an ISE is encouraged since it will allow a more expansive presentation within all the domains of efficacy analysis as presented in the "Integrated Summary of Effectiveness, Guidance for Industry"

Meeting Discussion

None

Question 10:

Does the Division agree with SKLSI's proposal not to write individual interim CSRs for the ongoing, uncontrolled, open-label studies (open-label extensions of Studies YKP3089C013 and YKP3089C017 and Study YKP3089C021)?

FDA Response to Question 10:

We are in agreement with your plan for studies YKP3089C013 and YKP3089C017. However, due to the more focused critical safety issue of hypersensitivity addressed by study YKP3089C021, an interim CSR is requested in section 5.3.5.1.

Meeting Discussion

None

Question 11:

Does the Division agree with SKLSI's proposal for how to provide the safety data from the ongoing studies for the NDA submission and for the 4-month safety update?

FDA Response to Question 11:

We are in agreement with your plan to provide safety data from ongoing studies with the exception of study YKP3089C025. In section 5.3.5.1, enter the line listings of SAEs, deaths, discontinuations, and AE of special interest from this study in a folder; in addition, hyperlink the respective adverse event forms to these line listings. Include this data in the April 2018 data cut off and the 4 month safety update.

Meeting Discussion

None

Question 12:

Does the Division agree with the proposed pooling and analysis strategy for the ISS and the Phase 1 studies that will be included in the cenobamate NDA?

FDA Response to Question 12:

The pooling plan is acceptable. Also see "General Clinical Safety Requests" below.

Meeting Discussion

None

Question 13:

Does the Division agree with SKLSI's proposal for analysis and presentation of the C-SSRS data?

FDA Response to Question 13:

Your plan for the suicidality data is acceptable.

Meeting Discussion

None

Question 14:

Does the Division agree with SKLSI's proposal to use MedDRA version 20.0 for both the NDA submission and the 4-month safety update?

FDA Response to Question 14:

Yes.

Meeting Discussion

None

NDA Format and Structure

Question 15:

Does the Division agree with SKLSI's proposal for providing the case report forms (CRFs) and patient narratives?

FDA Response to Question 15:

In general, your proposal seems appropriate. See the "Narratives and Case Report Forms (CRFs)" section of "General Clinical Safety Requests" presented below.

Meeting Discussion

None

Question 16:

Does the Division agree with SKLSI's proposal to provide financial disclosure certification in the cenobamate NDA?

FDA Response to Question 16:

Yes, your proposal to provide financial disclosure information for all clinical investigators who participated in studies YKP3089C013, YKP3089C017, and YKP3089C021 appears acceptable, at this time, based on the available information.

Meeting Discussion

None

Question 17:

Does the Division agree with SKLSI's proposal for submitting references in the cenobamate NDA?

FDA Response to Question 17:

Yes, if, in addition, you include active hyperlinks from the lists of references or citations to the referenced article.

Meeting Discussion

None

Regulatory and Labeling

Question 18:

Does the Division agree that the results of Studies YKP3089C013, YKP3089C017 and YKP3089C021 provide adequate justification for cenobamate dose recommendation (including starting and maximum) for the treatment of patients with partial onset seizures?

FDA Response to Question 18:

If your NDA is approved, the appropriate dose recommendations and titration for labeling will be a review issue.

Meeting Discussion

None

Question 19:

Does the Division agree that a single PDUFA fee for an original New Drug Application would support (b) (4) ?

FDA Response to Question 19:

Please note (b) (4) On face, it appears that your approach for monotherapy dosing and labeling is reasonable. Be sure your application addresses all the issues discussed in our Advice letter dated September 14, 2016,

Meeting Discussion

None

Question 20:

Is the Division able to determine at this time the likelihood the cenobamate NDA will be the subject of an Advisory Committee meeting?

FDA Response to Question 20:

Determination of the need for an Advisory Committee meeting will be a review issue.

Meeting Discussion

None

General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.

2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.

2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment.

3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.

5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:

    a. Title of the table or figure in the application
    b. A hyperlink to the location of the table or figure with page number
    c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)

6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.

7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.

9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).

10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

11. Provide the following tables related to exposure:

Sample Table A: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Healthy volunteers			
Controlled trials conducted for this indication[2]			
All other trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			
All other trials conducted for other indications			

[1] *Study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension from

randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

Sample Table B. Duration of Exposure

Dosage	Number of patients exposed to the study drug:				
	>= 1 dose	>=6 months[1]	>=12 months	>=18 months	18 months or longer
Dose 1	N=	N=	N=	N=	N=
Dose 2, etc.	N=	N=	N=	N=	N=

[1] These time interviews are provided as a sample. Time interval and cumulative treatment duration selected for this table will vary among products and should be based on experience with a specific product under review

12. Provide a list that includes the NCT number (for the ClinicalTrials.gov site) for each trial included in the submission.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for

whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.

3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C
- Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
   k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Condition Specific Requests: Epilepsy

1. Please identify and report all subjects with falls (by unique subject ID and study day number). Please also categorize all subjects with falls on the basis of whether they occurred with or without concurrent seizures. In addition, identify and report all injuries (in the SOC injuries and the MedDRA SMQ Accidents and Injury) in the same manner.
2. Perform an analysis of subjects who fit the search criteria for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) using the search criteria provided in Appendix 1 of this letter.
3. Clarify what criteria were used to categorize a seizure as an adverse event (versus lack of efficacy.)

Appendix 1: Updated List of MedDRA Search terms for identification of DRESS (MedDRA Version 13.1 – please update PTs with MedDRA version in current application)[1]

Modified RegiSCAR criteria for DRESS[2]

Reaction suspected to be drug related with
1. Acute skin rash
2. Involvement of at least one internal organ
3. Enlarged lymph nodes of at least two sites
4. One of the following blood count abnormalities (as reference you should use the limits provided by the lab that has done the analysis)
   - lymphocytes above or below the lab limits
   - eosinophils above the lab limits (in % or absolute count)
   - platelets below the lab limits
5. Fever above 38°C

(At least 3 of these criteria should be present for HSS/DRESS)
Please include events that occurred within 30 days of each other.

Source: http://regiscar.uni-freiburg.de/diseases/dress/index.html

1. ACUTE SKIN RASH

Skin and subcutaneous tissue disorders SOC

Dermatitis (any Preferred Term that includes the word dermatitis)
Drug eruption
Eczema
Erythema multiforme
Erythema nodosum
Rash (any PT that includes the word rash)
Skin lesion
Skin reaction
Skin exfoliation
Stevens-Johnson Syndrome
Toxic epidermal necrolysis

[1] MedDRA version 13.1. Some PT may be mentioned in more than one SOC.
[2] There should be certain temporal proximity for the onset of these AE (within 1 month of each other).

Toxic skin eruption
Urticaria

2. INVOLVEMENT OF AT LEAST ONE INTERNAL ORGAN

Blood and lymphatic disorders SOC:

Agranulocytosis
Aplastic anaemia
Aplasia pure red cell
Autoimmune lymphoproliferative syndrome
Autoimmune neutropenia
Autoimmune pancytopenia
Blood disorder
Bone marrow disorder
Bone marrow failure
Bone marrow toxicity
Coagulopathy
Disseminated intravascular coagulation
Drug rash with eosinophilia and systemic symptoms
Eosinophilia
Febrile neutropenia
Granulocytopenia
Hemolytic anemia
Hemolysis
Hypereosinophilic syndrome
Leukemoid reaction
Leukopenia
Lymphocytosis
Lymphopenia
Leukocytoclastic vasculitis
Lymphadenitis
Lymphadenopathy
Lymphoma
Monocytosis
Mononucleosis
Neutropenia
Pancytopenia
Platelet disorder
Platelet toxicity
Splenitis
Splenomegaly
Splenosis
Thrombocytopenia

Cardiac disorders SOC
- Autoimmune myocarditis
- Cardiomyopathy
- Endocarditis
- Eosinophilic myocarditits
- Myocarditis
- Pericarditis
- Pericardial effusion
- Pericardial disease
- Pleuropericarditis

Endocrine disorders SOC
- Adrenalitis
- Autoimmune thyroiditis
- Thyroiditis

Eye disorders SOC
- Eye allergy
- Eye swelling
- Iritis
- Iridocyclitis
- Optic neuritis
- Retinitis
- Uveitis
- Vitritis
- Scleritis

Gastrointestinal disorders SOC
- Allergic colitis
- Colitis
- Eosinophilic colitis
- Eosinophilic esophagitis
- Gastritis
- Gingival edema
- Gingival swelling
- Gingivitis
- Glossitis
- Ileitis
- Mouth ulceration
- Mesenteritis
- Oedema mouth
- Oropharyngeal swelling
- Parotitis
- Pancreatitis
- Periodontitis
- Sialoadenitis

Stomatitis
Swollen tongue
Tongue oedema
Vasculitis gastrointestinal

Hepatobiliary disorders SOC

Autoimmune hepatitis
Blood amylase increased
Blood trypsin increased
Cholangitis
Cholecystitis
Hepatic failure
Hepatic functional abnormal
Hepatic encephalopathy
Hepatic infiltration eosinophilic
Hepatitis
Hepatitis acute
Hepatitis toxic
Hepatocellular injury
Hepatomegaly
Hepatosplenomegaly
Hepatorenal failure
Hepatorenal syndrome
Hepatotoxicity
Hyperbilirubinaemia
Hyperlipasaemia
Jaundice
Liver disorder
Lipase abnormal
Lipase increased
Oedema due to hepatic disease
Oedematous pancreatitis
Pancreatic enzymes increased
Pancreatic haemorrhage
Pancreatic necrosis
Pancreatitis (any PT that includes the word pancreatitis)
Pancreatorenal syndrome
Peripancreatic fluid collection
Swollen tongue

General disorders SOC

Influenza like illness
Malaise
Multiorgan failure

Immune system disorders SOC

- Allergic bronchitis
- Allergic cough
- Allergic cystitis
- Allergic keratitis
- Allergic oedema
- Allergic sinusitis
- Alveolitis allergic
- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactoid reaction
- Asthma
- Angioedema
- Antiphospholipid syndrome
- Autoimmune disorder
- Autoimmune hepatitis
- Biliary cirrhosis primary
- Bronchospasm
- Circumoral oedema
- Cholangitis sclerosing
- Dermatomyositis
- Drug hypersensitivity
- Drug induced hypersensitivity
- Encephalitis
- Encephalopathy allergic
- Eyelid oedema
- Eosinophilic fasciitis
- Face oedema
- Hypersensitivity
- Idiopathic thrombocytopenic purpura
- Glomerulonephritis
- Laryngeal oedema
- Lip oedema
- Lip swelling
- Myasthenia Gravis
- Myositis
- Nephrogenic systemic fibrosis
- Oedema mouth
- Panniculitis
- Pemphigus
- Pemphigoid
- Periorbital oedema
- Pruritus allergic
- Polymyositis
- Reaction to drug excipients
- Sarcoidosis

Serum sickness
Systemic lupus erythematosus
Systemic sclerosis
Type IV hypersensitivity reaction
Vasculitis (including organ vasculitis: cerebral, GI, renal, retinal, ocular pulmonary, etc)
Vitiligo

Investigations SOC

Hematologic
Any preferred term (PT) that reflects increased, decreased or abnormal MedDRA Haematologic investigations High Level Group Term (HLGT)

Hepatobiliary
Blood tests increased or abnormal
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bilirubin conjugated
- Blood amylase
- Blood bilirubin
- Blood bilirubin unconjugated
- Gamma-glutamyltransferase increased
- Lipase
- Liver function test
- Transaminases

Biopsy liver abnormal

Immunologic
Any PT that reflects a positive or abnormal result under MedDRA Immunology and allergy investigations HLGT, and Investigations, imaging and histopathology procedures NEC, HLGT

Lung Biopsy lung abnormal

Renal
Blood creatine increased or abnormal
Blood urea increased or abnormal
Creatinine renal clearance decreased
Glomerular filtration rate decreased
Blood urine
Cells in urine
Eosinophils urine
Protein urine
Red blood cells urine
Urinary casts
Urinary casts present

Biopsy kidney abnormal

Skin Biopsy skin abnormal

Musculoskeletal and connective tissue disorders
- Arthralgia
- Arthritis
- Arthropathy
- Joint swelling
- Joint warmth
- Lupus-like syndrome
- Myopathy
- Myositis
- Polyarthritis
- Tendonitis
- Tenosynovitis
- Synovitis
- Any PT under the MedDRA Connective tissue disorder HLGT.

Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC
- Lymphoma (any kind of lymphoma)
- Pseudolymphoma

Nervous system disorders SOC
- Acoustic neuritis
- Arachnoiditis
- Central nervous system inflammation
- CNS ventriculitis
- Epiduritis
- Encephalitis (all PTs under Encephalitis NEC, High level term [HLT])
- Encephalopathy
- Leukoencephalitis
- Leukoencephalomyelitis
- Meningitis (all PTs under Meningitis NEC, HLT)
- Myelitis
- Neuritis cranial
- Neuropathy
- Polyneuropathy
- Reye's syndrome
- Toxic optic neuropathy
- Vasculitis cerebral

Renal and urinary disorders SOC
- Anuria
- Cardiorenal syndrome
- Dialysis

Eosinophilic cystitis
Haematuria
Haemodialysis
Haemolytic uraemic syndrome
Hepatorenal failure
Hepatorenal syndrome
Pancreatorenal syndrome
Peritoneal dialysis
Oedema due to renal disease
Renal disorder
Renal failure
Renal impairment
Renal toxicity
Any PT under MedDRA Nephropathies HLGT

Respiratory, thoracic and mediastinal disorders SOC

Allergic bronchitis
Acute interstitial pneumonitis
Asthma
Allergic granulomatous angiitis
Alveolitis
Alveolitis allergic
Angiolymphoid hyperplasia with Eosinophilia
Eosinophilic bronchitis
Eosinophilia myalgia syndrome
Eosinophilic pneumonia
Interstitial lung disease
Pleural effusion
Pleurisy
Pleurisy viral
Pleuropericarditis
Pneumonitis
Pulmonary eosinophilia
Pulmonary vasculitis
Pulmonary toxicity

Vascular disorders SOC

Arteritis (any PT that includes the word arteritis)
Capillaritis
Vasculitis (any Pt that includes the word vasculitis)

3. ENLARGED LYMPH NODES IN AT LEAST TWO SITES

Search term: Lymphadenopathy
It may be alone or as part of other PTs: Lymphadenopathy Mediastinal
Paratracheal

Generalised
Retroperitoneal
Vaccination site

Include other PT that could reflect lymphadenopathy:
- Benign lymph node neoplasm
- Lymph node palpable
- Lymph node scan abnormal

4. **ONE OF THE FOLLOWING BLOOD COUNT ABNORMALITIES**
   -LYMPHOCYTES ABOVE OR BELOW LAB LIMITS
   -EOSINOPHILS ABOVE THE LAB LIMITS
   -PLATELETS BELOW LAB LIMITS

   In addition to these, there are multiple potential hematologic manifestations of DRESS that were included under Internal Organ involvement

5. **FEVER ABOVE 38° C**

- Hyperthermia
- Hyperpyrexia
- Pyrexia
- Febrile bone marrow aplasia (and all PTs that include the word "febrile")

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

The handout used by the sponsor at the meeting is attached

7.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 24, 2018 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, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. 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 https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.				
2.				

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site,* in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is

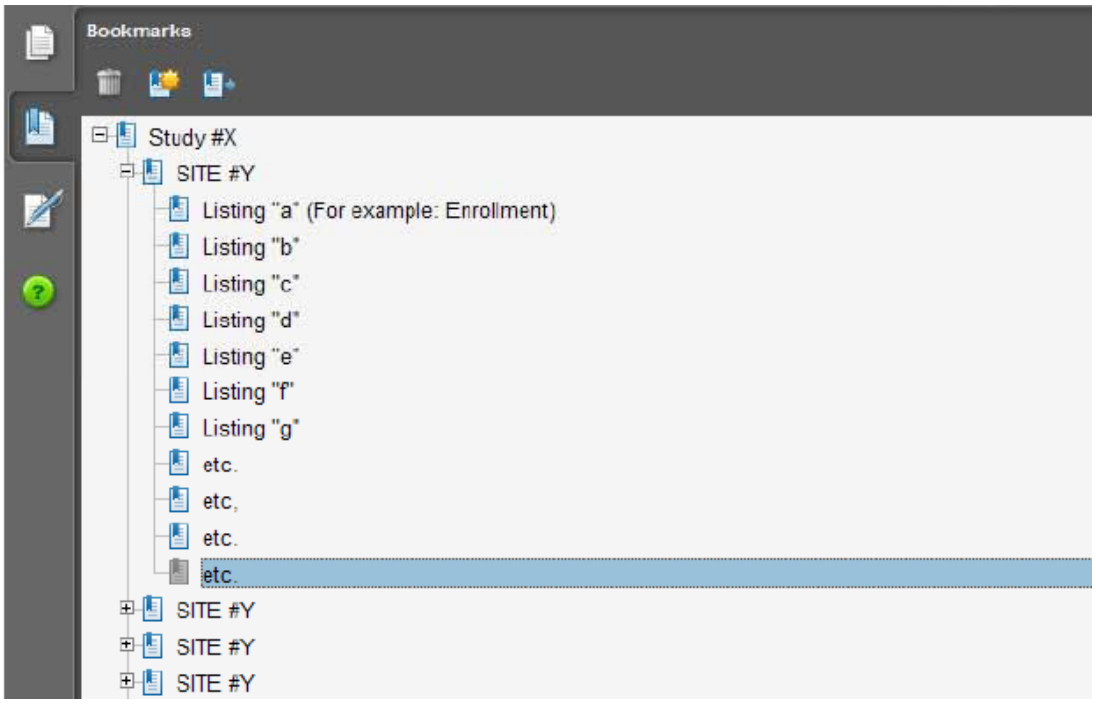
maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[3]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[3] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

9 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
05/03/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076809

MEETING MINUTES

PPD, US Agent for SK Life Science, Inc.
Attention: Myriam Antoun
Director, Development Solutions, Global Regulatory Affairs
PPD
3900 Paramount Parkway
Morrisville, NC 27560

Dear Ms. Antoun:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YKP3089.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on October 1, 2015.

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

If you have any questions, call Hamet Touré, PharmD MPH, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Thursday, October 1, 2015, 1100 to noon
Meeting Location: White Oak, Building 22, Room 1419
Application Number: IND 076809
Product Name: YKP3089
Indication: Adjunctive treatment of partial onset seizures
Sponsor/Applicant Name: SK Life Science, Inc.

Meeting Chair: Billy Dunn, MD
Meeting Recorder: CDR Hamet Touré

FDA ATTENDEES

Division of Neurology Products
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Clinical Team Leader
Norman Hershkowitz, MD, Clinical Team Leader
Steven Dinsmore, MD, Clinical Reviewer
Edward Fisher, PhD, Nonclinical Reviewer
Annalise Anise, PharmD Candidate
Hamet Touré, PharmD, Project Manager

Office of Clinical Pharmacology
Angela Men, MD, PhD, Team Leader
Ta-Chen Wu, PhD, Reviewer

Office of Biostatistics
Xiang Ling, PhD, Reviewer

Division of Pediatrics and Maternal Health
Denise Johnson-Lyles, PhD, Project Manager
Donna Snyder, MD, Reviewer
BeLinda Hayes, PhD, Pharmacologist

Controlled Substance Staff
Silvia Calderon, PhD, Pharmacologist
Martin Rusinowitz, MD, Medical Officer

SPONSOR ATTENDEES

SK Life Science, Inc.
Marc Kamin, MD, Chief Medical Officer
Hong Wook Kim, PhD, Director, Clinical Safety
Palanichamy Ilankumaran, PhD, Clinical Study Manager
Mark Friesen, Head of Project Management
Susan Melnick PhD, Associate Director Safety and Toxicology
Jeong Woo Cho, PhD, Chief Operating Officer

PPD
Myriam Antoun, Director of Regulatory Affairs

1. BACKGROUND

The meeting is an End-of-Phase 2 meeting for YKP3089. The purpose of the meeting is for SK Life Science, Inc. to share the results of completed non-clinical and clinical YKP3089 studies with FDA. The objective of the meeting is for the sponsor to obtain feedback regarding non-clinical and clinical YKP3089 development plans for the NDA submission.

FDA sent Preliminary Comments to SK Life Science on September 29, 2015.

2. DISCUSSION

The sponsor's questions are reproduced below and FDA preliminary responses follow each question.

Question I: Does the Agency concur with the following?

1. The total set of completed non-clinical pharmacology and toxicology studies, along with final reports from the mouse and ongoing rat carcinogenicity studies, comprise a complete package for a New Drug Application filing of oral YKP3089 for the proposed indication.

   FDA Preliminary Response:

   On face, the completed and ongoing nonclinical studies appear sufficient for an NDA; however, the adequacy of the studies will be a matter of review.

   Sponsor's Response to FDA Preliminary Response: We agree.

   Meeting Discussion: None

2. The completed genetic toxicity, fertility and embryo-fetal development toxicity studies are adequate and no further studies are required.

   FDA Preliminary Response:

   See response to Question 1 above.

   Sponsor's Response to FDA Preliminary Response: We agree.

   Meeting Discussion: None

3. The completed pre/post-natal development toxicity study and on-going juvenile rat toxicity study are sufficient to support the conduct of the proposed clinical trials in the pediatric population.

   FDA Preliminary Response:

If the ongoing juvenile rat study is determined to be adequate upon review and raises no additional safety concerns, it should be sufficient to support the conduct of the clinical trials in pediatric patients.

Sponsor's Response to FDA Preliminary Response: SK would like to understand under what mechanism would the FDA wish SK to submit the results of the juvenile rat study as well as the timeline for FDA review and feedback of these results.

Meeting Discussion: The Division stated that the juvenile rat study final report should be submitted to the IND as a nonclinical information amendment and that, while not required, some period of review time (days) should be provided as a courtesy prior to initiation of clinical trials in pediatric patients. In response to the sponsor's inquiry, the Division responded that an audited draft report would be acceptable, provided that it is complete. The sponsor agreed to submit its audited study report for the Division's review prior to the initiation of its proposed clinical trials in the pediatric population.

4. The completed preclinical abuse liability studies are sufficient.

   FDA Preliminary Response:

   See response to Question VI.

Question II: Does the Agency agree that no further Phase 1 studies may be required other than the completed studies and planned studies for NDA application?

FDA Preliminary Response:

- If the clinical and TBM formulations differ significantly, formulation bridging between these two will need to be established and food effect may be needed to be evaluated with the TBM formulation.

  Sponsor's Response to FDA Preliminary Response: SK would like to better understand the need for a food effect study with the TBM.

  The clinical and TBM formulations are not different and no further formulation bridging studies are needed because:

  - A capsule formulation was used in the first adequate and well controlled efficacy clinical study (YKP3089C013);
  - The TBM formulation was used in the second adequate and well-controlled clinical study (YKP3089C017);
  - The capsule and TBM formulations were shown to be bioequivalent in Study YKP3089C019.

Additionally a food effect study with the TBM formulation is not needed because:

- No food effect was observed with the capsule formulation (Study AA39450);
- The capsule and TBM formulations were shown to be bioequivalent in Study YKP3089C019;
- TBM and capsule are both immediate-release formulation therefore no food effect is expected.

Meeting Discussion: The sponsor clarified that the formulations administered in the two pivotal efficacy trials were taken either with or without food. The Division agreed that in this case a food effect study with the TBM formulation was likely unnecessary, and that the acceptability of the results of the aforementioned trials in this respect would be a matter of review. The Division also indicated that food intake should be included as a covariate in the planned population PK analysis, a point to which the sponsor agreed.

- The PK properties/activity of the major/active metabolite(s) will need to be characterized in the NDA submission.

Sponsor's Response to FDA Preliminary Response: SK would like to provide additional context regarding PK properties/activity of YKP3089 metabolites. SK did not find any major metabolite (>10% AUC according to the 2008 FDA Guidance). There is only one YKP3089 metabolite (M1) detectable in human plasma and the PK of this metabolite has been characterized using radioactive methodology. The M1 metabolite is a glucuronide and is present in plasma at <2% of total AUC of the dose. Glucuronides are generally pharmacologically inactive. Therefore, further PK and activity characterization are not needed.

To facilitate this discussion we are attaching a section from a recent submission to the IRT (Apr2015,Serial #123, Page 1-3) that provides further details about the metabolite of YKP3089, in the event that the division has an opportunity to review in advance of tomorrow's meeting.

att. "Evaluating the relationship between plasma concentrations of metabolites (as appropriate) and QTc".

Meeting Discussion: Based on the sponsor's response to the Division's preliminary meeting comments, the Division agreed that further characterization of the PK properties/activity of the major metabolite(s) would not be necessary.

- To support dosing recommendations, you should explore the exposure-response relationship and assess the potential impact of gender and race.

Sponsor's Response to FDA Preliminary Response: We agree.

Meeting Discussion: None

- You should provide a rationale in your NDA for not including a mild renal impairment group in the proposed renal impairment study and not including a severe hepatic impairment group in your proposed hepatic impairment study.

  Sponsor's Response to FDA Preliminary Response: We agree.

  Meeting Discussion: None

- We note a lack of inclusion of elderly subjects in the completed studies. You should evaluate the impact of age on the PKs and drug exposure.

  Sponsor's Response to FDA Preliminary Response: We agree.

  Meeting Discussion: None

Question III: Does the Agency agree that no further DDI studies may be required other than the completed studies and planned studies for NDA application?

FDA Preliminary Response:

On face, the proposed DDI studies seem reasonable. Please assess the contribution from each major CYPs and UGT enzymes to the metabolism of YKP3089. Since details of the completed and planned studies, as well as the planned population PK analyses, are not available, the final acceptance of these DDI studies will be a matter of review.

Sponsor's Response to FDA Preliminary Response: We agree.

Meeting Discussion: None

Question IV: Will the efficacy results from the two completed adequate and well-controlled studies be sufficient to support an NDA submission for the proposed indication with a target dose of 200 mg/day?

FDA Preliminary Response:

Yes, the efficacy data provided appear sufficient to support the filing of an NDA.

Sponsor's Response to FDA Preliminary Response: We agree.

Meeting Discussion: None

Question V: Will the proposed safety database be sufficient for NDA filing?

FDA Preliminary Response:

The proposed safety database appears adequate for filing. However, the ultimate acceptability of the dataset will depend upon the extent to which it can adequately define the safety signals of concern, which will be a matter of review.

Sponsor's Response to FDA Preliminary Response: We agree.

Meeting Discussion: None

Question VI:

1. Based on the available nonclinical and clinical data collected for YKP3089, does the Agency agree that the abuse and dependence potential signals are limited? Does the Agency recommend the conduct of a human abuse potential study?

FDA Preliminary Response:

No. We cannot agree that the abuse and dependence potential of the drug are limited, because we have not reviewed final protocols and we have not received full reports for the drug discrimination, self-administration or physical dependence studies. As we previously communicated, the design of behavioral studies to characterize the discrimination cues and reinforcing properties of a drug with an unknown mechanism of action is challenging. We also requested you to include in your report an assessment of the observed metabolic profiles between species in the overall evaluation of the abuse potential of YKP3089, and an assessment of how the plasma levels achieved in the animal studies correlated to plasma levels achieved in humans at therapeutic doses.

Sponsor's Response to FDA Preliminary Response: SK will submit the full reports for the non-clinical drug abuse study for CSS review in 4Q2015. How long is the CSS' typical timeframe review and feedback? These reports will address the species differences in metabolic profiles and how the plasma levels achieved in the animal studies correlate to the plasma levels at human therapeutic doses.

Meeting Discussion: The Division encouraged the sponsor to submit its full final study reports to the IND to facilitate the Agency's Abuse Liability Assessment analysis. The Agency indicated that it may provide general comments about these reports, but will defer review of the data until the submission of the NDA.

Regarding the conduct of a human abuse potential study, although it could be the most reasonable path to follow, the administration of supratherapeutic doses in the context of these studies raise safety concerns. So, at this time, these studies are not recommended until further safety information is collected.

Sponsor's Response to FDA Preliminary Response: Regarding the conduct of a human abuse potential study, SK has not identified any safety concerns that would preclude conducting a single dose human abuse liability study at doses up to a supratherapeutic

level of 600mg. SK is prepared to conduct a human abuse liability study if such a study would provide the required information in the most efficient manner.

Meeting Discussion: The Agency noted that it generally expects that human abuse potential studies evaluate doses that are two to three times the maximum recommended therapeutic dose. The sponsor stated that in their experience single dose administration of doses of YKP3089 as high as 600mg could be administered safely. The Agency requested that the sponsor submit the study protocol and information to support the proposed dose of YKP3089 for review.

Additionally, we recommend further exploration of YKP3089's receptor binding to include all known receptors associated with abuse.

Sponsor's Response to FDA Preliminary Response: SK has reviewed the guidance referenced by the CSS and can confirm that the required neurotransmitter systems of interest have been conducted and no significant receptor binding was observed. This information is captured in the Investigator's Brochure however detailed reports of studies SK-YC-01 has been provided in the original IND submission and PHARM-NJ-SM-19 was subsequently provided.

SK would, therefore, like to better understand the CSS' recommendation.

Meeting Discussion: The Agency and the sponsor agreed that the briefing package did not provide a complete list of neurotransmitters and that the sponsor should submit binding data for review.

2. Given the limited signals of withdrawal and dependence, does the Agency agree that the evaluation of dependence and withdrawal can be conducted as part of the continued phase 2/3 clinical program in lieu of a stand-alone study?

FDA Preliminary Response:

No. We do not agree for the reasons stated above. We recommend assessing dependence at the end of a clinical study, even with its limitations. We suggest submitting such a draft protocol for CSS review and comments.

Sponsor's Response to FDA Preliminary Response: SK would like to better understand the CSS' recommendation regarding the evaluation of dependence. In general, anti-epileptic drugs should not be abruptly discontinued in patients with epilepsy because of the risk of increased seizure frequency and status epilepticus. Evaluating withdrawal and dependence is therefore challenging in this population. As well, in clinical practice, withdrawal and dependence would not occur in epilepsy patients because dosing is tapered.

Meeting Discussion: The Agency recommended that the sponsor conduct the dependence/withdrawal study in healthy volunteers in whom the drug should be

discontinued abruptly after 4 weeks of achieving a maintenance dosage of 200 mg daily (not including the up-titration period). The Agency also asked the sponsor to attempt to differentiate adverse events that led to a withdrawal of treatment from adverse events that were the results of a withdrawal.

3. SKLSI would like to receive the CSS's feedback regarding the abuse liability evaluations.

FDA Preliminary Response:

We request that you consider the feasibility of conducting a self-administration study in monkeys since a human abuse potential study may not be possible. We know that the metabolic profile of YKP3089 is the same in monkeys and humans, and there is vast information regarding the self-administration of depressants such as benzodiazepines and barbiturates in this species.

Sponsor's Response to FDA Preliminary Response: This discussion relates to Question VI (1), para.2 above. In SK's opinion, human studies are preferred approach over monkey studies.

Meeting Discussion: The Agency agreed that human abuse potential studies are preferred and would negate the need to conduct a study in monkeys.

Question VII: SKLSI would like to receive the Division's preliminary feedback regarding inclusion of adolescent age group in the NDA application provided an adequate number of adolescents are studied.

FDA Preliminary Response:

You propose an open-label safety study, with collection of population based pharmacokinetic (PK) sampling to confirm dosing, in approximately 100 pediatric patients with partial onset seizures (POS). You propose that efficacy will be established by fully extrapolating efficacy from the adult population. We will review your argument after you submit your Initial Pediatric Study Plan.

Sponsor's Response to FDA Preliminary Response: We agree.

Meeting Discussion: The sponsor stated that it plans to submit the adolescent study protocol for review prior to study initiation. The Division reminded the sponsor to submit its initial Pediatric Study Plan (iPSP) within 60 days of the End-of-Phase 2 meeting.

3. ADDITIONAL FDA COMMENTS

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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 draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
10/14/2015