CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209521Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107645

MEETING PRELIMINARY COMMENTS

Allergan, Inc.
Attention: Jillian McCumber, MS
Director, Global Regulatory Affairs
2525 Dupont Drive, P.O. Box 19534
Irvine, CA 92623-9534

Dear Ms. McCumber:

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

We also refer to your correspondence dated and received November 2, 2016, requesting a meeting to discuss the development plan for sarecycline tablets for the treatment of acne vulgaris.

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, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Senior Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 11, 2017, 9:00 AM – 10:00 AM EST
Meeting Location: Teleconference

Application Number: IND 107645
Product Name: sarecycline tablets
Indication: for the treatment of acne vulgaris
Sponsor Name: Allergan, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 11, 2017, 9:00 AM – 10:00 AM EST via teleconference between Allergan, Inc. and the Division of Dermatology and Dental Products. 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. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (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

Meeting Purpose

The purpose of the meeting is to discuss the development plan for sarecycline tablets

Regulatory Correspondence History

We have had the following meetings with you:

- Written Responses – January 30, 2012
- Written Responses – June 30, 2010

We have sent the following correspondences:

- Advice – August 20, 2015

- Pediatric Study Plan Initial Agreement – April 3, 2015
- Advice – February 10, 2015
- Pediatric Inadequate Study Request – December 19, 2014
- Pediatric Study Plan Written Response – December 19, 2014
- Advice – July 22, 2014
- SPA Request Denied – May 27, 2014
- End-of-Phase 2 Final Responses – May 14, 2014
- Advice – May 7, 2014
- Advice – November 25, 2013
- Advice/Information Request – September 5, 2013
- SPA Agreement (Nonclinical) – July 18, 2012
- Advice – June 22, 2012
- Advice/Information Request – June 22, 2011
- Advice/Information Request – October 18, 2010
- Advice/Information Request – August 31, 2010

2.0 DISCUSSION

2.1. Regulatory

Question 1:

Allergan considers sarecycline to be a New Chemical Entity (NCE) and intends to file NDA 209,521 in accordance with PDUFA V legislation using a 505(b)(1) pathway.

Does the Agency agree that sarecycline will be considered an NCE and should be filed under PDUFA V?

FDA Response to Question 1:

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

Question 2:

Sarecycline is a novel tetracycline that may have similar characteristics to other tetracycline derivatives. The safety profile of the tetracycline class of antibiotics is well known and adequately characterized within the literature and postmarketing reports. Tetracycline derivatives are a well-established chemical class that are approved in the United States, including several approved for indications pertaining to acne vulgaris, and have been available on the market since the 1960's (Doxycycline – 1967, Minocycline – 1971). Given

the body of data that exists for tetracycline derivatives, Allergan proposes that an Advisory Committee is not necessary for the sarecycline NDA.

Does the Agency agree that an Advisory Committee will not be required for NDA 209,521?

FDA Response to Question 2:
Decisions regarding the need for Advisory Committee discussion will not be made until NDA submission and filing reviews have been completed.

However, we currently are not aware of any novel or complex regulatory issues that would necessitate Advisory Committee discussion at this stage of development.

Question 3:
A draft eCTD Table of Contents (TOC) for NDA 209,521, including details on the planned submission of specific study reports for Module 4 and Module 5, is provided in Appendix 1.

Does the Agency agree that the proposed organization of the submission is acceptable?

FDA Response to Question 3:
From a technical standpoint (not content related) yes, the proposed organization of the submission is acceptable. However, please see additional comments below:

- m1.6.3 Correspondence regarding meetings – a single pdf file of all meeting documents can be provided (instead of individual pdf files) with proper bookmarks, table of contents and hyperlinks
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.
- Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF, including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located here:- http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf
- For datasets and structure, please visit the Study Data Standards Resources Webpage, located at: http://www.fda.gov/forindustry/datastandards/studydatastandards/ and the Study Data Technical Conformance Guide, located here: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf.
- Case report forms need to be referenced under the appropriate study's STF, organized by site as per the specifications and tagged as "case report form".

Provide leaf titles that are clear and indicative of the content (e.g. "Section 1, Question1" is not a clear leaf title

Question 4:

Allergan plans to generate a pooled analysis for both efficacy and safety (an Integrated Summary of Efficacy [ISE] and an Integrated Summary of Safety [ISS]). The text portions of the ISS and ISE will be placed in Module 2, Sections 2.7.3 and 2.7.4, respectively. Summary tables and data listings of the pooled data, along with the respective SAPs, will be provided in Module 5, Section 5.3.5.3.

Does the Agency agree with this proposal?

FDA Response to Question 4:

The integrated summary of efficacy (ISE) and integrated summary of safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports and are required by the regulations to be located in Module 5. If you believe Section 2.7.3 (Summary of Clinical Efficacy) and Section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISE and ISS, respectively, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, a description of the contents of each section should be included in both Module 2 and Module 5{21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a)}. Provide electronic links in Module 2 to the tables and figures in Module 5.

For additional information about the location of ISS and ISE in the CTD, refer to guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at the FDA website.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

Question 5:

For all phase 2 and phase 3 studies in which at least one group was treated with sarecycline capsule at a dose of 1.5 mg/kg/day (PR-10411.1, SC1401, SC1402, and SC1403), Allergan plans to provide electronic case report forms (eCRFs) for the following categories of study participants: deaths, serious adverse events (SAEs), severe adverse events (severe AEs), and discontinuations for any reason. Based on *ICH E3, Structure and Content of Clinical Study Reports (CSRs)*, Allergan proposes that the CRFs be organized and submitted by study in Module 5.3.5.1. All eCRFs will have their respective study's accompanying study tagging file.

Does the Agency agree with this proposal?

FDA Response to Question 5:

Your proposal to submit CRFs in the application is acceptable.

Question 6:

For all phase 2 and phase 3 studies in which at least one group was treated with sarecycline capsules at a dose of 1.5 mg/kg/day (PR-10411.1, SC1401, SC1402, and SC1403), Allergan

intends to include narratives for deaths, SAEs, severe AEs, and discontinuation due to AEs within each CSR submitted with the NDA and also in Module 5.3.5.3, as a separate file separated by event type (ie. death, SAE, discontinuation due to AE), and study number.

Does the Agency agree with this proposal?

FDA Response to Question 6:
Your proposal is acceptable.

Question 7:
The draft Target Product Profile (TPP) is provided to facilitate a structured dialogue with the Agency to communicate Allergan's direction for potential label claims and to reach an understanding of the FDA's thinking on various aspects of the sarecycline Clinical Development Program. This proposed TPP for the treatment of inflammatory lesions of moderate to severe acne vulgaris is provided in Appendix 8.

Does the Agency have any comments on the proposed sarecycline Target Product Profile (TPP)?

FDA Response to Question 7:
The Agency has no specific comments on the Target Product Profile provided by the sponsor pending review of the clinical trial data. The appropriateness of the terminology for the indication in labeling will be considered during the review. Labeling negotiations will be conducted after a complete review of the NDA submitted to the Agency.

Question 8:
At the time of the NDA submission, the phase 3 clinical trials will have been completed. No additional trials are currently planned to be initiated during the NDA review period. Allergan plans to submit a literature review and a cover letter stating that there are no new data available in lieu of the 120-day safety update.

Does the Agency agree with this proposal?

FDA Response to Question 8:
Your proposal is acceptable provided all safety data from your Phase 3 clinical trials and the long-term extension safety data is included with the initial NDA submission.

2.2. Chemistry, Manufacturing and Controls

Question 11:
In the Agency's EOP2 final response letter dated 14 May 2014, the Agency did not agree (b) (4)

(b) (4)

(b) (4)

Based on this information, does the Agency agree (b) (4) (b) (4) *for sarecycline hydrochloride drug substance?*

FDA Response to Question 11:

Your proposal (b) (4) appears reasonable. An overview (b) (4) should be included in the NDA or in the referenced DMF(s). The (b) (4) specifications should be justified based on this manufacturing process (b) (4) (b) (4)

Question 12:

During the EOP2 Meeting, Allergan provided rationale (b) (4) (b) (4)

Does the Agency concur with the additional scientific justification [redacted] *?*

FDA Response to Question 12:

[redacted]

Question 13:

Allergan intends to submit in the NDA the stability data package outlined in Table 11 to support the following:

- [redacted] commercial drug substance manufacturing sites.
- [redacted] commercial drug product manufacturing site.

Does the Agency agree that the intended NDA stability data package is adequate to support [redacted] *as commercial drug substance manufacturing sites, and also* [redacted] *as the commercial drug product manufacturing site?*

FDA Response to Question 13:

Your proposed plan for submission of the drug substance stability package appears to be acceptable. Note that any stability test limits should be established at identical levels to the drug substance release specifications. Results for all specified and unspecified impurities should be reported.

The drug product stability data package outlined in the briefing package appears reasonable to support your NDA submission.

Question 14:

At the EOP2 Meeting held on 23-Apr 2014, the Agency agreed that the microbiology data appeared to be adequate. Studies to characterize the microbiological profile of sarecycline have focused on the following: confirmation of mode of action, assessing antibacterial activity against clinical isolates of *Propionibacterium acnes* (including strains with high-level resistance to erythromycin), spectrum of activity studies against Gram-positive and Gram-negative bacteria, in vitro resistance development studies, proof of concept efficacy in tissue-based infection models, and evaluation of anti-inflammatory properties in a rat carrageenan-induced footpad edema model.

Does the Agency agree that the completed microbiology studies are sufficient to enable filing and review of the sarecycline NDA?

FDA Response to Question 14:

The data appear adequate for the filing of the NDA. However, this does not preclude the possibility of requests for additional information or clarifications as the assessment of the submission progresses.

Additional CMC Comments

The peak resolutions described for the [redacted] (b) (4) peaks and the [redacted] (b) (4) peaks for the related substance release HPLC method do not appear to be adequate. Specificity will need to be demonstrated in your final HPLC method validation package.

The long-term stability conditions you are using to evaluate the drug substance retest period [redacted] (b) (4) would not support storage [redacted] (b) (4) We recommend revising the proposed storage conditions [redacted] (b) (4)

The current proposed [redacted] (b) (4) limit (NMT [redacted] (b) (4) ppm) and batch levels ([redacted] (b) (4) ppm) observed for the [redacted] (b) (4) drug substance exceeds the typical ICH Q3C limit ([redacted] (b) (4) ppm). A justification for this limit should be provided.

A description of the control strategy [redacted] (b) (4) should be provided.

2.3. Pharmacology/Toxicology

Question 19:

The proposed organization of Module 4 will be presented in the table of contents (TOC) provided in the meeting information package. The nonclinical development program to support the new formulation for the pivotal phase 3 clinical studies was agreed with the Agency at the EOP2 Meeting held on 23-Apr-14.

Does the Agency agree with the proposed organization of Module 4?

FDA Response to Question 19:

Yes, we agree. However, we note that there is a typo under Subtitle 4.2.3.4.1 of Module 4. The two carcinogenicity studies should be a 104-week oral carcinogenicity study in rats and a 104-week oral carcinogenicity study in mice, respectively.

Note that in order to enable us to conduct statistical review of the carcinogenicity studies, in addition to providing final study reports, SAS tumor data sets (tumor.xpt) of the two studies should also be provided in the NDA submission. The standard format for preparing the data is provided (Attachment 2) for your reference.

Question 20:

As recommended by the Agency in the EOP2 Meeting Minutes dated 14-May-2014, Allergan has performed Quantitative Stucture Activity Relationship (QSAR) analysis (DEREK and Leadscope) for all the drug substance impurities that exceed the ICH Q3A(R2) qualification threshold. [redacted] (b) (4) The drug substance impurities

have been adequately qualified in the rat and monkey repeat-dose oral toxicity studies and in either the in-vitro bacterial mutation and chromosomal aberration studies and/or via the DEREK and Leadscope QSAR analyses. The drug substance impurity levels in the lots used in the toxicology studies and lots used to manufacture the phase 3 clinical batches are provided in Section 11.3.1.

Does the Agency agree that the impurities have been adequately qualified?

FDA Response to Question 20:

The summary toxicology information appears reasonable for the qualification of the identified drug impurities. Submit all supporting data, not just summary information, to the NDA for review. The final determination of the data adequacy to support the impurity specifications will be made during the NDA review.

2.4. Clinical Pharmacology

Question 21:

Allergan has completed the 14 phase 1 studies listed in Table 12.

Does the Agency agree that the completed clinical pharmacology studies are sufficient to enable filing and review of the sarecycline NDA?

FDA Response to Question 21:

The completed clinical pharmacology trials appear reasonable to support filing of your NDA application. In your NDA, provide the following information:

1. Provide in a tabular format a list of all the formulations used in the clinical trials and clearly indicate which trials used the to-be-marketed formulation.
2. Submit all bioanalytical method validation and bioanalysis reports and include information to support the long term storage stability of the pharmacokinetic (PK) samples. Also provide incurred sample reanalysis reports.
3. Submit all PK data sets in in XPT format.
4. Drug interaction assessments of parent and major metabolites.
5. Provide information of the activity of the metabolites.

Question 22:

Allergan has completed the additional recommendations the Agency provided in the EOP2 Meeting Minutes (14 May 2014) for Clinical Pharmacology. Additional details will be provided in the Meeting Information Package.

Does the Agency agree that the additional recommendations provided in the EOP2 Meeting Minutes (14 May 2014) for Clinical Pharmacology have been adequately addressed?

FDA Response to Question 22:

The Clinical Pharmacology development program appears reasonable to support the filing of your NDA application. The adequacy of data will be reviewed at the time of your NDA submission.

2.5. Clinical/Biostatistics

Question 9:

In Allergan's development program, 378 healthy study participants have been exposed to sarecycline during phase 1 studies, 212 study participants have been exposed to sarecycline during phase 2 Study PR-10411, and an estimated 1,000 study participants will be exposed to sarecycline in the pivotal phase 3 studies (SC1401 andSC1402), plus additional study participants in the long-term safety extension study (SC1403) who received placebo in the pivotal trials. Allergan anticipates an estimated 380 to400 study participants with 6-month (24-week) exposure and an estimate of approximately 180 study participants with 12-month (52 week) exposure, consistent with ICH guidance of 300 to500 study participants with 6-month exposure and 100 study participants with 12-month exposure.

Does the Agency agree that the subject exposure is sufficient to support the overall safety database for filing and review of the sarecycline NDA?

FDA Response to Question 9:

It appears that you may have sufficient safety data for your NDA application. Whether the safety data submitted supports the overall safety conclusions in the risk/benefit analysis is a review issue.

Question 10:

Allergan has observed site-specific lesion count data anomalies at one site participating in the pivotal phase 3 study SC1402 and long-term safety extension study SC1403 – Site 211, Principal Investigator Dr. Francisco Flores, FXM Research Miramar, located at 14601 SW 29th Street, Suite 208, Miramar, FL 33027. Due to concerns over the efficacy data integrity for Dr. Flores' site, Allergan has made the decision to exclude all study participants randomized at the site (31 study participants) from the intent-to-treat (ITT) and per-protocol (PP) analyses for Study SC1402. All study participants seen at Dr. Flores' site will be included in the safety analyses for the NDA because there were no noted anomalies with safety-related parameters.

Does the Agency agree with this proposal?

FDA Response to Question 10:

It is difficult to concur with your proposal without having full details on the extent of the violations and the available data for each individual subject including treatment assignment. We recommend you conduct a sensitivity analysis investigating the impact of inclusion/exclusion of this site on the efficacy results. Determination on how to handle subjects from Site 211 will be a review issue.

Question 15:

Allergan proposes to provide the following summary level clinical site data as described in the FDA draft guidance for industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning*, and the associated technical

specifications in the document *Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning*, for the pivotal phase 3 studies SC1401 and SC1402 as part of the sarecycline NDA.

General study-related information and comprehensive clinical investigator information will be provided as part of the initial sarecycline NDA for both pivotal phase 3 clinical studies (or referenced if provided elsewhere in the submission):

1. General study-related information:
    a. Site number
    b. Principal Investigator
    c. Site Location: Address (eg, Street, City, State, Country) and contact information (ie, phone, fax, email)
    d. Location of Principal Investigator: Address (eg, Street, City, State, and Country) and contact information (ie, phone, fax, email).
2. Study participant information by site:
    a. Number of study participants screened at each site
    b. Number of study participants randomized at each site
    c. Number of study participants treated who prematurely discontinued for each site by site
3. Study conduct and documentation information:
    a. Location at which sponsor study documentation is maintained (eg, monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8).
    b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical studies and brief statement of study-related functions transferred to them.
    c. The location at which study documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained.
4. Sample annotated eCRFs, original protocols, and all protocol amendments will be provided in the final CSRs.

Site-specific individual study participant level data listings for the specific sites requested will be provided upon request during NDA review for each pivotal phase 3 clinical study:

1. Listing for each study participant consented/enrolled; for study participants who were not randomized to treatment and/or treated with study therapy, this will include the reason not randomized and/or treated
2. Study participant listing for treatment assignment (randomization)
3. Listing of study participants that discontinued from study treatment and study participants that discontinued from the study completely (ie, withdrew consent) with date and reason discontinued
4. Listing of PP study participants/non-PP study participants and reason not PP

5. By-study participant listing of eligibility determination (ie, inclusion and exclusion criteria)
6. By-study participant listing of AE, SAEs, deaths and dates
7. By-study participant listing of significant protocol violations and/or significant deviations reported in the NDA, including a description of the deviation/violation
8. By-study participant listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, the raw data listings used to generate the derived/calculated endpoint will be provided.
9. By-study participant listing of concomitant medications (as appropriate to the pivotal clinical studies)
10. By-study participant listing of testing (eg, laboratory, electrocardiogram [ECG]) performed for safety monitoring

Significant deviations/violations (as listed above) are defined as those protocol deviations/violations that are likely to have an impact on the study participant's rights, safety, well-being, and/or on the validity of the data for analysis (defined as *major* for the phase 3 studies).

Does the Agency agree with the proposed submission plan for summary level clinical site data?

FDA Response to Question 15:

Please see the attached OSI information request for the specific data listings requested. Also, OSI requests that this information be submitted for all clinical sites involved in the pivotal Phase 3 studies.

Question 16:

Allergan has conducted 14 phase 1 studies; one phase 2 study; 2 identical, pivotal, phase 3 placebo-controlled studies; and a long-term safety study to support the NDA submission for sarecycline. Allergan plans to integrate the 2 pivotal phase 3 studies and provide pooled results for the ISE. The phase 1 and phase 2 studies will not be part of the integrated analysis because the design, treatment exposures, endpoints, and objectives of those studies were different than the pivotal phase 3 studies.

For the ISS, Allergan plans 2 pooled safety populations:

1. Study participants from the 2 identical, pivotal phase 3 placebo-controlled studies (SC1401 and SC1402) and from the 1.5 mg/kg/day or placebo arms in the phase 2 study (PR-10411) to provide valid placebo-controlled comparisons with the 1.5 mg/kg/day dose, and
2. All sarecycline study participants who received the 1.5 mg/kg/day dose in the phase 2 study (PR-10411), the 2 pivotal phase 3 studies (SC1401 and SC1402), or the long-term safety study (SC1403).

The proposed SAPs for the ISS and ISE will be provided in the Meeting Information Package.

Does the Agency agree with the integration strategy for the analysis for the ISS and ISE?

Does the Agency have any additional recommendations on the proposed SAPs for the ISS and ISE?

FDA Response to Question 16:

Your proposed integration strategy for the ISS and ISE appears reasonable.

Question 17:

Allergan plans to submit the following for each study of the 2 pivotal phase 3 studies (SC1401 and SC1402) and the long-term safety extension study (SC1403) in the NDA:

1. Study Data Tabulation Model (SDTM) dataset definition file
2. Analysis dataset (ADS) definition file
3. SDTM data SAS transport file
4. ADS SAS transport files
5. Annotated eCRFs

The draft SDTM dataset definition file (item #1), draft ADS definition file (Item #2), and annotated eCRFs (Item #5) for protocol SC1401 are provided in the Appendices section. The data definition documents and annotated eCRFs for Study SC1402 will be identical to those for Study SC1401. The ADS(s) and ADS definition file from the ISE and ISS will be submitted in the NDA. The ADS and tables, listings, and graphs are developed by using SAS programs which will be available upon request by the Agency.

Does the Agency agree with the proposed package of datasets and the corresponding documentation to be provided in the proposed NDA?

FDA Response to Question 17:

Your proposal to submit study datasets in accordance with Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide 3.1.2 (CDISC-SDTM IG 3.1.2) is acceptable. In addition, your proposal to submit analysis datasets based on CDISC Analysis Data Model Implementation Guide 1.0 version is acceptable. In addition to the pivotal Phase 3 trials, we request such datasets be submitted for your Phase 2 trial (PR-10411).

The primary method for handling missing efficacy data in your Phase 3 trials is the Multiple Imputation (MI) approach, which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in

more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Additional Comment:
You do not plan to conduct any analyses for non-inflammatory lesions. Your application should include analyses for non-inflammatory lesions to determine whether there is worsening in non-inflammatory lesions with the application of your product. In addition, your application should include the non-inflammatory lesion count data.

Question 18:
The pivotal phase 3 studies SC1401 and SC1402 SAPs currently indicate in Section 10.1.1 that tests of normality (D'Agostino's Skewness and Kurtosis tests, D'Agostino 1990) will be conducted prior to determining whether the primary analysis model will be parametric – using an analysis of covariance (ANCOVA) model with the actual data, or nonparametric – using an ANCOVA model with ranked data. However, due to the large sample sizes in these studies, even small deviations from normality are likely to result in these tests of normality being rejected. Instead, it is proposed to update the SAPs for these studies in a blinded fashion prior to database lock, such that the parametric model will be used for the primary analysis and the nonparametric approach will be performed as a sensitivity analysis.

The revised SAP for SC1401 is provided in Appendix 3. The proposed changes are identical for SC1402.

Does the Agency agree with this proposal to use the parametric approach as the model for the primary analysis while shifting the nonparametric approach to be one of the sensitivity analyses?

FDA Response to Question 18:
Your proposal to have the nonparametric approach as a sensitivity analysis for the primary parametric approach appears reasonable. Your application should include detailed discussion if the two approaches produce different conclusions.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 21, 2016 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 V. 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. 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.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.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 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.

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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

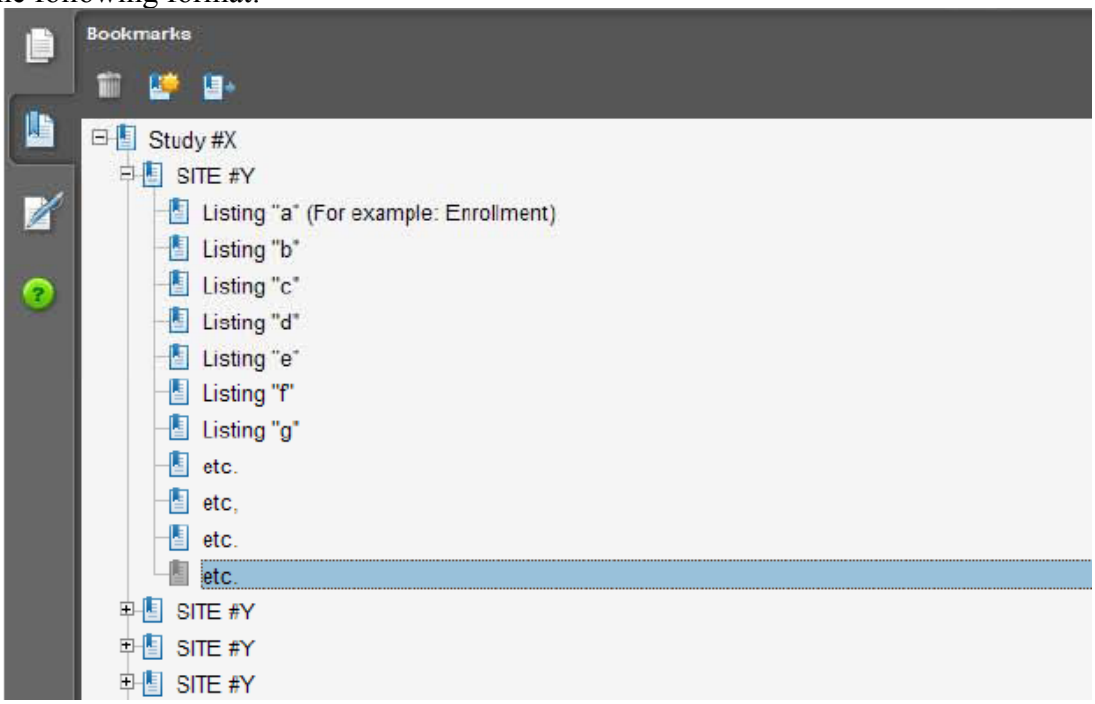
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

    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[1]	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.

[1] 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

Attachment 2

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's May 2015 guidance document titled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*".

The tumor dataset should be prepared in the following format:

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,.. in ascending order from control to highest dose group	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value coded with a dot (.) should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4677, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

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

/s/

OMOLARA R LAIYEMO
01/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND107645

MEETING MINUTES

Warner Chilcott (US), LLC
Attention: Wei Zhuang
Senior Manager, Regulatory Affairs
100 Enterprise Drive
Rockaway, NJ 07866

Dear Ms. Zhuang:

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

We also refer to the meeting scheduled on April 23, 2014 between representatives of your firm and the FDA. The purpose of the meeting was to discuss the development plan for (sarecycline) tablets (b) (4) Your premeeting briefing package (March 21, 2014) provides background and questions for discussion.

We acknowledge the email on April 22, 2014, notifying us that after receipt and review of the premeeting communication consisting of Agency responses to your questions, you have determined that the responses to your questions are sufficient and additional discussion is not necessary.

This letter and the enclosed final responses represent the official record.

If you have any questions, call Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL RESPONSES

IND: 107645

Product: (sarecycline) tablets

Regulatory Path: 505(b)(1)

Sponsor: Warner Chilcott Company, LLC

Proposed Indication: (b) (4)

Type of Meeting: Type B, End-of-Phase 2

Meeting Date: April 23, 2014

Introductory Comment:
This material includes the Agency's final responses to the questions submitted for your meeting scheduled for April 23, 2014, at 9:00 AM via teleconference between Warner Chilcott (US), LLC and the Division of Dermatology and Dental Products. This material was shared to promote a collaborative and successful discussion at the meeting. After receipt of the preliminary responses, you had two options:

- If these answers and comments were clear to you and you determined that further discussions were not required, you had the option of canceling the meeting.
- If you determined that discussion was needed for only some of the original questions, you had the option of reducing the agenda.

You conveyed to Strother D. Dixon via email on April 22, 2014 that the responses to your questions were sufficient and additional discussion was not necessary. As such, the below responses represent our final responses to your questions.

Purpose of the Meeting:
To discuss the development program for (sarecycline) tablets

Regulatory Correspondence History

We have had the following meeting with you:
- Written Responses – January 30, 2012

- Written Responses – June 30, 2010

We have sent the following correspondences:
- Advice – November 25, 2013
- Advice/Information Request – September 5, 2013
- SPA Agreement (Nonclinical) – July 18, 2012
- Advice – June 22, 2012
- Advice/Information Request – June 22, 2011
- Advice/Information Request – October 18, 2010
- Advice/Information Request – August 31, 2010

General Agency Comments:
Our meeting responses are based on the briefing document and we have not completed review of your final study report of the Phase 2 dose ranging trial. We are concerned that we have identified certain issues that may impact the conclusion that treatment effects of your proposed dosing regimen have been adequately evaluated in Phase 2. We are not confident that you have identified a dosing regimen most likely to succeed in Phase 3.

The impact of subject outliers, the applicability of fixed dose regimen in your Phase 2 trial to the weight based dosing in Phase 3, and the variable success rates according to subject baseline disease severity lead us to recommend additional Phase 2 dose ranging prior to agreements on your Phase 3 trials.

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Does the Division agree (b) (4)

Response:
No, we do not agree. (b) (4) You may provide the information in the NDA or reference to a DMF with letter of authorization.

Provide complete establishment information for all facilities (b) (4) in the proposed NDA with a statement of readiness for inspection for each facility.

Question 2:
Does the Division concur with the rationale (b) (4) ?

Response:
Yes, we agree (b) (4)

Question 3:
Warner Chilcott has completed extensive characterization studies [redacted] Does the Division agree that no further polymorph characterization studies are needed for NDA submission?

Response:
Yes, we agree.

Question 4:
Does the Division agree that the potential effect of process changes on the sarecycline HCl drug substance have been adequately assessed and appropriate controls and specifications are in place to assure drug substance of intended quality for the planned clinical studies?

Response:
No, we do not agree because (1) impurity characterization results for the new process are not included in the briefing package for review, and (2) we have comments for the acceptance criteria of related substances (see the response to Question 5).

Question 5:
Does the Division agree with the proposed release and stability testing plan for sarecycline HCl drug substance to support the planned clinical studies?

Response:
No, we do not agree. The proposed limits for impurities are not consistent with ICH Q3A guidance, which are as follows:

- Reporting threshold of [redacted]%
- Identification threshold of [redacted]%, and
- Qualification threshold of [redacted]%

Several impurities with limits above ICH qualification threshold do not seem to be qualified. The assay limit of [redacted]% is broad and will require justification.

Question 6:
Does the Division concur with the proposed release and stability testing plan for sarecycline tablets to support the planned clinical studies?

Response:
Yes we agree.

Note that for the NDA the identification based on retention time only is not considered specific enough.

Additional CMC comment:
Clarify whether you have applied for a USAN name for sarecycline HCl.

Pharmacology/Toxicology

Question 7:
Does the Division concur that the drug substance impurities that exceed the ICH Q3A(R2) qualification threshold have been adequately qualified in the rat and monkey repeat-dose oral toxicity studies and in either the in vitro bacterial mutation and chromosomal aberration studies or via the DEREK and Leadscope QSAR analyses?

Response:
No, we do not concur. Overall, your approach to qualify the impurities identified in the drug substance appears reasonable. However, the following additional information is needed. Perform QSAR analysis (Derek and Leadscope) (b) (4) and perform QSAR analysis (Leadscope) (b) (4) Provide the actual impurity levels in the toxicology lots with which you calculated the dose of impurity at NOAEL. Provide impurity level comparison between the lots used for pivotal toxicology studies and the clinical lots.

Question 8:
Does the Division concur that the nonclinical studies conducted to date support the proposed Phase 3 studies including the proposed dose and duration up to 12 months, and that those studies along with the ongoing studies are sufficient to enable filing and review of the sarecycline NDA?

Response:
The proposed clinical dose (1.5 mg/kg/day) and treatment duration for the two Phase 3 clinical trials (12 weeks) and for the open-label long-term safety study (up to 52 weeks) are supported by nonclinical data.

We acknowledge that a pre- and post-natal development study in rats and 2-year carcinogenicity studies in mice and rats are ongoing. Your nonclinical program appears adequate to support submission of a NDA for sarecycline. However, the final determination of the adequacy of your nonclinical data to support a NDA will be made after review of all the full study reports submitted to your NDA.

Clinical Pharmacology

Question 9:
Does the Division concur that the completed and planned clinical pharmacology studies are sufficient to enable filing and review of the sarecycline NDA?

Response:
Your overall Clinical Pharmacology plan appears reasonable. However, we have the following comments:

1. Provide data to support the proposed dosing based on body weight. You need to substantiate that body weight has an effect on your product's pharmacokinetics (PK).
2. Your Phase 3 trial will use a new formulation compared to what was used in your Phase 2 dose finding trial. We recommend that you complete the relative bioavailability trial between the new tablet formulation and the capsule formulation prior to initiating your

Phase 3 trials so that dose finding and other clinical trial results from Phase 1 and 2 trials could be used to inform dosing in Phase 3.

3. We recommend that you evaluate the effect of food on the PK of the tablet formulation before initiating your Phase 3 trial to inform dosing.
4. Because you are proposing body weight based dosing, you should address the dosage strength proportionality of the new tablet formulation.
5. We note that the inhibitory potential of CYP2B6 and CYP2C8 was not evaluated. You should evaluate the inhibitory potential of CYP2B6 and CYP2C8 in-vitro and based on the results, you should evaluate the need for further in-vivo assessment as recommended by *Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012)*.
6. You should adequately characterize PK in the pediatric population you intend to treat.

Clinical/Biostatistics

Question 10:
Does the Division agree that Phase 2 study results support the selection of the 1.5 mg/kg/day dose for further evaluation in the Phase 3 program?

Response:
See General Agency Comments above. From a clinical and nonclinical safety standpoint, we do not object to the 1.5 mg/kg/day dose. Whether your dosing regimen is optimized is not clear given the limited treatment effects on lesion counts and the lack of a clear dose response relationship in your Phase 2 trial. The impact of outliers, subject weight ranges, and disease severity balance across treatment arms may affect the utility of conclusions from this trial.

Question 11:
Does the Division agree with the proposed Phase 3 development plan, including the study designs, variable and endpoint selections (particularly the IGA for inflammatory acne as a co-primary endpoint for the placebo controlled efficacy studies), sample size, analysis population definitions, statistical methodology, and safety assessments?

Response:
See above comments regarding your proposed dosing regimen.

Your proposed Investigator's Global Assessment (IGA) is a 6-point scale; whereas the IGA recommended by the Agency is a 5-point scale with success defined as a score of "Clear" or "Almost Clear" and at least a 2-point improvement from Baseline. The preference for a 5-point assumes the scale is linear (i.e., equal length categories), a 2-point reduction on a 5-point scale is more clinically meaningful than that on a 6-point scale. In addition, or enrollment criteria, a specific minimum score implies a slightly higher severity on the 5-point scale compared with that on the 6-point scale. In addition, clarify why descriptors in your proposed Phase 3 IGA are different from your Phase 2 IGA scale. This will have an effect on your treatment estimates for Phase 3 trials planning.

The following are general comments regarding the submitted draft Phase 3 protocol (SC1401):

- You plan to investigate the treatment-by-site interaction using the Breslow-Day test for the IGA endpoint and using an interaction term in the ANCOVA model for the change in inflammatory lesion counts endpoint; however, you did not provide the planned number of sites. To allow for a meaningful investigation of the site-to-site variability, each site should enroll a reasonable number of subjects per treatment arm (e.g., 8 subjects). In addition, the Agency recommends the randomization be stratified by site to ensure balance across the treatment arms within each site. The protocol should include the complete details on how the randomization will be carried out and pre-specify an algorithm for pooling small site if the actual enrollment does not meet the minimum number of subjects per treatment arm per site.

- The primary analysis population should be the intent-to-treat (ITT) population, defined as all randomized subjects regardless if they had at least one post-baseline efficacy assessment.

- You plan to use LOCF as the primary imputation method for handling missing data. As the scientific justification for using LOCF is weak, you should provide an adequate rationale for using LOCF or propose a more scientifically sound method (e.g., multiple imputation). In addition, you should pre-specify sensitivity analyses that utilize alternate assumptions to those in the primary imputation method, to ensure that the results are not driven by the method of handling missing data.

- Since certain oral contraceptives have a defined treatment effect on acne lesions, your statistical analysis plan should include distinct analyses that examine the subjects treated with oral contraceptives separately from the total ITT population.

- As the results of your QT assessments have not yet been submitted for review, you should include adequate cardiovascular screening and monitoring during future trials to insure safety of subjects.

However, with the trend toward earlier age of onset of adrenarche and menarche, there appears to be a downward shift in the age at which acne vulgaris first appears. You may wish to consider an inclusion/exclusion criterion that allows subjects under the age of 12 years with acne that meets your other lesion count criteria. If you intend to request a partial waiver for pubertal adolescents under 12 years, your Pediatric Study Plan should include data on the incidence, prevalence, and product use to support your rationale that studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed) in the population for which you seek a partial waiver.

Question 12:
Does the Division agree that the proposed subject exposure (both number of subjects and intermittent duration of use) is sufficient to support the overall safety database for filing and review of the sarecycline NDA?

Response:
Yes, your proposed number of subjects and duration of exposure appears reasonable to support the overall safety database.

Question 13:
Does the Division concur that the completed microbiology studies are adequate to enable filing and review of the sarecycline NDA?

Response:
The data at this stage appear to be adequate. Any additional data acquired in Phase 3 with relevance to microbiology should be submitted in order to support the NDA.

Question 14 and Question 15:
Does the Division concur with the plan to propose a waiver for children ages 0 to (b) (4) years in the NDA for the pediatric study requirement?

Does the Division concur (b) (4)

Response:
Sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting. 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. See comments on PREA requirements below.

Question 16
Does the Division concur that the clinical studies conducted to date and those planned are adequate, depending upon the results, to enable filing and review and review of the sarecycline NDA?

Response:
See above discussion.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of

protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests.

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/s/

STANKA KUKICH
05/14/2014