CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213433Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 112137

MEETING MINUTES

Cassiopea SpA
C/o: Ground Zero Pharmaceuticals, Inc.
Attention: Evan B. Siegel, PhD
President and CEO
5405 Alton Parkway, Suite A-464
Irvine, CA 92604

Dear Dr. Siegel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for clascoterone cream, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on May 6, 2019. The purpose of the meeting was to discuss the content and format of the proposed NDA submission for clascoterone cream, 1%.

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

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 6, 2019; 10:30am
Meeting Format: Teleconference

Application Number: IND 112137
Product Name: clascoterone cream, 1%
Proposed Indication: For the topical application for the treatment of acne vulgaris in patients 9 years of age or older
Sponsor Name: Cassiopea SpA

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Patricia Brown, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III)
Soo Hyeon Shin, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biostatistics III (DB III)
Carin Kim, PhD, Biostatistics Reviewer, DB III

SPONSOR ATTENDEES

Luigi Moro, Chief Scientific Officer
Alessandro Mazzetti, Chief Medical Officer
Roberta Bozella, Regulatory Manager, Cosmo
Enrico Fragasso, Clinical Project Manager
Carmen Pirozzolo, NDA Program Coordinator
(b) (4) Toxicologist Scientific Advisor, (b) (4)
(b) (4) Medical Consultant
(b) (4) Statistical Consultant and (b) (4)
(b) (4) Statistical Consultant, (b) (4)
Evan Siegel, CEO, Ground Zero Pharmaceuticals, Inc.
Jean Siegel, Medical Writer, Ground Zero Pharmaceuticals, Inc.

1.0 BACKGROUND

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- February 17, 2015 End of Phase 2 Final Written Responses

We have sent the following correspondences:

- April 8, 2019 Proprietary Name Granted
- March 23, 2018 Advice/Information Request
- October 26, 2016 Advice
- April 27, 2016 Harmonized Annual Report Due Date Granted
- March 25, 2016 Advice
- March 22, 2016 Advice
- December 15, 2015 Pediatric Study Plan- Initial Agreement
- July 30, 2015 Special Protocol-Agreement
- June 22, 2015 Pediatric Study Plan- Written Response
- May 18, 2015 Special Protocol- No Agreement
- February 26, 2014 Advice
- January 8, 2014 Special Protocol- Agreement (carcinogenicity)
- February 1, 2013 Advice
- August 1, 2012 Advice
- May 30, 2012 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 12:
The draft NDA table of contents for Modules 4 and 5, showing all nonclinical and clinical reports is provided in Attachment 2. Does the Division have any comments or further suggestions?

FDA Response to Question 12:
The division has no further comments.

Question 13:
We plan to incorporate the ISE/ISS text within Sections 2.7.3 and 2.7.4 in Module 2 and include the additional source tables in Module 5.3.5.1 (Section 15.6.2). Does the Division agree with this proposed plan?

FDA Response to Question 13:

Although the guidance for industry: *Integrated Summary of Effectiveness* allows for the case where the narrative portion of the integrated summaries are placed in Module 2 with supportive appendices in Module 5, the guidance also states this approach to be feasible for relatively simple drug development programs. You are encouraged to include a full ISE in Module 5 with appropriate summaries in Module 2. Note that the ISE should include discussions regarding the strength of evidence across all studies, including discussion of any difference in outcomes across studies.

We recommend the same general approach for the ISS.

Question 14:
We plan to include eCRFs and narratives for deaths, other serious adverse events, and discontinuations due to adverse events. Does the Division agree with this proposed plan?

FDA Response to Question 14:
Your plan is generally acceptable.

Provide narratives for all deaths, serious adverse events (SAEs) regardless of causality, subjects who discontinued the study product due to adverse events (AEs), hypersensitivity/drug reactions, and pregnancies. These narratives may also be included in the Clinical Study Reports (CSRs) with links to the narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety

Question 15:
While Cassiopea has obtained financial disclosure information from investigators in all of the clinical studies, based on 21 CFR 54.2e, we plan to include this information in the NDA for the investigators in Studies CB-03-01/33 (TQT study), 171-7151-202 and CB-03-01/28 (HPA axis suppression studies), 171-7151-201 (dose response), and CB-03-01/25 and CB-03-01/26 (pivotal efficacy).

Does the Division agree?

FDA Response to Question 15:
Your proposal appears acceptable.

Question 16:
Following NDA approval of clascoterone, Cassiopea proposes standard postmarketing safety reporting per 21 CFR 600.80 and not having a risk evaluation and mitigation strategy (REMS) for this new chemical entity. The rationale for that is provided in Section 15.6.4.

Does the Division agree?

FDA Response to Question 16:
At this time, it appears that a REMS will not be required; however, this will be a review issue when the NDA is submitted.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1:
On the basis of the storage conditions applied during clinical development, [redacted] (b) (4) does the Division agree with the following storage conditions proposed for commercial drug product and approved for some products already on the market?

FDA Response to Question 1:
The storage condition for commercial drug product will be determined based on data from the primary stability registration batches of drug product. The data from the clinical batches will only be used as additional supporting stability data. For clinical trial material, we recommend the following storage conditions:

Storage the product in a refrigerator at 2°C and 8°C (36°F and 46°F) prior to dispending. Do not freeze.

Store the product while in use at room temperature 25°C (77°F). Discard the unused product 180 days after the date of dispensing.

However, we will determine appropriate storage conditions and expiration dating period for the drug product based on stability data from the primary stability registration batches of drug product during the review of your NDA.

Question 2:
The NDA will include a letter of authorization to refer to the DMF for the active pharmaceutical ingredient and we plan to cross-reference the DMF and not include Section 3.2.S in the NDA.

The NDA will include Section 2.3.S. Does the Division agree with this proposed plan?

FDA Response to Question 2:
Complete drug substance information should be provided either in the application or in a DMF. Appropriate Letter of Authorization for the review of the referenced DMF should be provided. If information is provided in a DMF, we request that the following information be provided in the NDA for ease of review: General information, physico-chemical properties (3.2.S.1), and Specifications (3.2.S.4). Please submit a Certificate of Analysis of the drug substance (3.2.S.4).

The applications need to include the appropriate prefix in the href links (e.g. xlink:href="../../indXXXXXX/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words “cross reference to” and the application number (e.g. Cross Ref to dmfXXXXXX). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

2.3. Non-Clinical

Question 3:
The nonclinical program includes the completed 9-month topical drug application toxicology study in minipigs with the cream formulation and the 2-year topical carcinogenicity study in rats with cortexolone 17-α propionate (CB-03-01). It also includes 28-day and 13-week toxicity studies (subcutaneous administration) in rats, an Ames test, and a chromosome aberration test in human lymphocytes with cortexolone 21-propionate, the main degradation product of CB-03-01.

Does the Division agree that this nonclinical program will support filing of the NDA?

FDA Response to Question 3:
Yes, we agree that the nonclinical program for cortexolone 17-α propionate will support filing of the NDA.

Question 4:
Because the nonclinical general toxicology and reproductive toxicology studies on CB-03-01 that will be submitted in this NDA were initiated and finalized prior to December 17, 2016, we believe that SEND files will only be required for the 2 most recent studies, A3234 and A3233, which are the 13-week rat toxicity study and the chromosome aberration study, both with the metabolite cortexolone 21-propionate.

Does the Division agree?

FDA Response to Question 4:
Yes, we agree that submitting SEND files for the two most recently conducted nonclinical studies only is acceptable.

2.4. Biostatistics/Clinical

Question 5:
Does the Division agree that this clinical program will support NDA filing?

FDA Response to Question 5:
In general, your program appears acceptable to support the submission of a New Drug Application (NDA) for clascoterone cream, 1% for the topical treatment of acne vulgaris in patients 9 years of age and older.

You propose a safety database wherein approximately 810 subjects will have experienced short-term exposure (twice a day for 12 weeks, P3 CB-03-01/25 & CB-03-01/26, P2 171-7151-201) to investigational drug, more than 300 subjects for 6 months, and more than 100 for one year. At this time, the safety database is acceptable. However, the safety database needed will depend on safety signals identified during your development program. Ultimately, the adequacy of your safety database will be a review issue.

We remind you to conduct a single point vasoconstrictor assay (VCA) with adequate bracketing to determine the potency classification of your product as recommended earlier during Pre-IND meeting on August 10, 2011 and End of Phase 2 meeting on February 17, 2015.

Meeting Discussion:
The sponsor was advised to conduct a VCA study to inform labeling. The Agency further clarified that lack of this study would not be a filing issue, and could be conducted as a postmarketing commitment.

Question 6:
The plan for pooling safety data is summarized in Section 15.4.2.

Does the Division agree with the proposed plan for the integrated summary of safety (ISS)?

FDA Response to Question 6:
You propose to create three sets of pooled data:

- Pool A: Phase 3 pivotal studies
- Pool B: Phase 1 and Phase 2 studies, by type of subject and treatment
- Pool C: CB-03-01 subjects only, by type of subject and planned extent of exposure

Pool A

Phase 3 Pivotal Studies						
Parameters	CB-03-01/25		CB-03-01/26		Total	
	CB-03-01 cream 1% BID (N=353)	Placebo (N=355)	CB-03-01 cream 1% BID (N=369)	Placebo (N=363)	CB-03-01 cream 1% BID (N=722)	Placebo (N=718)

Pool B

Parameters	Phase 1 (Healthy Volunteers)		Phase 1 & 2 (Acne Vulgaris)			Pooled CB-03-01 All Phase 1&2 Studies All Doses (N=745)
	CB-03-01 [1] (N=352)	Placebo [2] (N=14)	CB-03-01 [3] (N=393)	Placebo [4] (N=89)	Retin-A® 0.05% [5] (N=30)	

- Includes all CB-03-01 doses from Phase 1 studies with healthy subjects (i.e., all dose groups from the five Phase 1 studies with healthy subjects: CB-03-01/02, CB-03-01/04, CB-03-01/05, CB-03-01/32, CB-03-01/33).
- Includes Placebo only from Phase 1 studies with healthy subjects (i.e., CB-03-01/02, CB-03-01/33).
- Includes all CB-03-01 doses from Phase 1 and 2 studies with acne vulgaris subjects (i.e., 1% BID from 171-7151-202; 1% QD from CB-03-01/03; 0.1% BID, 0.5% BID, 1% QD, 1% BID from 171-7151-201; 1% BID from CB-03-01/28; 1% QD from 171-7151-203).
- Includes Placebo from Phase 2 studies 171-7151-201 and CB-03-01/03.
- Includes Retin-A from Phase 2 study CB-03-01/03.

- Includes CB-03-01 from all Phase 1 and Phase 2 studies, a pool of columns [1] and [3].

Pool C

Parameters	Phase 1 (Healthy Volunteers)		Phase 1&2&3 (Acne Vulgaris)					Pooled CB-03-01 All Studies All Doses [3]
	CB-03-01 [1]		CB-03-01 [2]					
	< 3 wks [4] N=66	≥ 3 wks [5] N=286	2 wks N=69	6-8 wks N=36	12 wks N=1010	> 12 wks N=607	Pooled N=1405	Pooled [6] N=1757

- Includes all CB-03-01 doses from Phase 1 Studies with healthy subjects (i.e., all dose groups from the five Phase 1 studies with healthy subjects: CB-03-01/02, CB-03-01/04, CB-03-01/05, CB-03-01/32, CB-03-01/33).
- Includes all CB-03-01 doses from all studies with acne vulgaris subjects: 1% BID from 171-7151-202; 1% QD from CB-03-01/03; 0.1% BID, 0.5% BID, 1% QD, 1% BID from 171-7151-201; 1% BID from CB-03-01/28; 1% QD from 171-7151-203; 1% BID from CB-03-01/25, CB-03-01/26 and CB-03-01/27.
- Includes CB-03-01 from all Phase 1, 2, and 3 studies, a pool of columns [1] and [2].
- Includes all CB-03-01 doses from studies with healthy subjects with planned extent of exposure <3 weeks: CB-03-01/02, CB-03-01/04, and CB-03-01/33
- Includes all CB-03-01 doses from studies with healthy subjects with planned extent of exposure ≥3 weeks: CB-03-01/05 and CB-03-01/32
- Includes CB-03-01/27, a long-term extension study where all subjects participated in either CB-03-01/25 or CB-03-01/26 previously

In general, pooling of subjects should be based on patient population, dose, and duration of treatment.

We agree with your proposal for Pool A to include two Phase 3 pivotal trials.

The rationale for your proposed Pool B appears unclear, since subjects include healthy volunteers and those with acne. Also included are subjects exposed to variable doses and variable duration of dosing. For Pool B we would recommend inclusion of subjects with acne, exposed to the same dose (1% BID) and duration of dosing (12 weeks) e.g. twice a day for 12 weeks, P3 trials CB-03-01/25 & CB-03-01/26 and P2 trial 171-7151-201.

The rationale for your proposed Pool C also appears unclear, since subjects include healthy volunteers and those with acne. Subjects are exposed to variable doses and variable duration of dosing. We would recommend that apart from Pool A above and recommended Pool B above, that all remaining trials be presented separately.

Meeting Discussion:
The sponsor agreed with the Agency recommended pooling strategy. In addition, the sponsor will provide a safety summary based on all subjects who receive study product regardless of the dose/frequency.

Question 7:
We plan to include pooled analyses of efficacy data from the 2 Phase 3 studies (CB-03-01/25 and CB-03-01/26) for the integrated summary of efficacy (ISE) (Section 15.4.3). The main objective of the ISE will be to explore efficacy of clascoterone in certain subgroups of patients, such as by age, gender, and Fitzpatrick skin type. Does the Division agree with the proposed plan for the ISE?

FDA Response to Question 7:
As the objective of the Integrated Summary of Efficacy (ISE) is to support the analysis results obtained from the individual trials, your planned exploratory pooled analyses of the Phase 3 trials appear reasonable. It should be noted that establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study finding.

Question 8:
For subgroup analyses by age in the ISS and ISE, (b) (4) we propose to use the categories of 9 to < 12, 12 to < 18, 18 to < 65, and ≥ 65 years of age (Section 15.4.3).

Does the Division agree with these proposed stratified age groups?

FDA Response to Question 8:
The proposed stratified age groups appear acceptable.

Meeting Discussion:
The sponsor clarified that no subjects over age 65 were enrolled in any of the trials.

Question 9:
For the planning of bioresearch monitoring (BIMO) inspections, Cassiopea plans to include tables and listings in the NDA as recommended in the February 2018 guidance on *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* for the two "pivotal" studies, CB-03-01/25 and CB-03-01/26, and the long-term extension study CB-03-01/27 (Section 15.4.4).

Does the Division agree with the proposed plans?

FDA Response to Question 9:
Yes, we agree with the proposed approach.

Question 10:
Study CB-03-01/28 contains pharmacokinetic data from pediatric subjects 9 to 12 years old with acne. Together with the results of the Phase 3 studies, which included subjects ≥ 9 years old, all of the planned studies outlined in Section 5 of the Agreed iPSP have been completed and all results will be included in the NDA.

Does the Division agree that, assuming the results presented in the NDA are positive, the iPSP commitments will have been fulfilled?

FDA Response to Question 10:
We acknowledge the Agreed Initial Pediatric Study Plan (Agreed iPSP) for topical treatment of acne vulgaris in patients 9 years of age and older (FDA agreement letter dated 12/15/2015). A partial waiver of pediatric subjects between the ages of 0 to 8 years is reasonable because the necessary studies are impossible or highly impracticable. However, whether additional studies in pediatric subjects ages 9 years and above will be required under PREA will be determined during review of the NDA.

Additional comments from Clinical Pharmacology:
In your NDA, submit the following:

1. Raw PK concentrations and calculated PK parameters for baseline corrected clascoterone concentrations should be submitted in SAS transport format for maximal use studies.
2. Bioanalytical method validation reports and bioanalysis reports should be submitted for all active moieties, metabolites as well as serum cortisol used for HPA axis suppression assessment.
3. Adequate long-term PK and cortisol sample storage stability data should be submitted.

Question 11:
Section 15.4.5 presents our proposal regarding the scope, format, and documentation of the electronic datasets and case report tabulations to be submitted.

Does the Division agree with the proposed approach regarding the scope, format, and documentation of the electronic datasets and case report tabulations?

FDA Response to Question 11:
Yes, from the technical standpoint the proposed approach is acceptable.
You stated that the clinical studies conducted with CB-03-01 were conducted prior to implementation of current CDISC standards for the data analysis and reporting for the clinical study reports (CSRs), and to comply with current CDISC standards for the submission, the data for all 13 studies will be converted to SDTM and/or ADaM formats. Submit both SDTM and ADaM datasets for Trials CB-03-01/25 and CB-03-01/26.

Submit the SAS code used to implement the multiple imputation (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, site ID, 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).

You are reminded of the Agency's previous comments (7/30/2015) that "for the secondary endpoints, while you proposed the absolute change as well as the percent change of total lesion counts in addition to the individual lesion types (i.e., noninflammatory, inflammatory), as the total lesion is a sum of the two types of lesion, such total lesion count endpoints might not provide additional information meaningful for labeling".

Additional comments:

1. At the time of NDA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

2. Include the full text version of any referenced articles.

3. The pooled analysis (Pool A: CB-03-01/25 & CB-03-01/26; recommended Pool B: P3 trials CB-03-01/25 & CB-03-01/25 and P2 trial 171-7151-201) should include the following:

    a. Summary Table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term reported by ≥1% of subjects for individual trials and pooled data sets

    b. Summary Table of Treatment-Emergent Treatment- Related Adverse Events (Adverse Reactions) by System Organ Class and Preferred Term reported by ≥1% of subjects for individual trials and pooled data sets

    c. Case report forms (CRFs) and narratives with corresponding electronic links as discussed above.

    d. Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)

e. Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

f. Shift tables for all vital signs. Provide the normal values for all parameters used in your analyses.

g. If the product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120 day safety update.

h. A comparison of safety results from the individual trials and pooled data.

i. Safety analyses in subgroups of subjects by sex, race, age group (>65 years versus < 65 years), and baseline severity

j. Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug

4. Provide a risk-benefit analysis for your proposed product in the context of available therapy.

5. Provide in the 120-day safety update, a summary of information which was not submitted in the NDA including the following:
   a. A detailed description of any significant changes or findings in the safety profile.

   b. A description of any information that suggests a substantial change in the incidence of common, but less serious adverse events.

   c. A summary of worldwide experience of safety of the proposed drug including an updated estimate of use for the drug marketed in other countries.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 20, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

Meeting Discussion:
The sponsor proposed a table identifying by study the site ID; PI name, address, contact information (phone, fax, email); and number of subjects randomized, and submitting that table along with Form 356h in Module 1.1. The Agency agreed with this proposal.

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

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

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

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific

standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission **"DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS"** in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA 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), you 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.				

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

/s/

KENDALL A MARCUS
05/06/2019 02:50:33 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 112137

MEETING MINUTES

Cosmo Dermatos Srl
c/o Therapeutics, Inc.
Attention: Garet Heintz, RAC
Associate Director, Regulatory Affairs
9025 Balboa Avenue, Suite 100
San Diego, CA 92123

Dear Mr. Heintz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cortexolone 17-α propionate cream, 1%.

We also refer to the meeting scheduled on January 28, 2015, between representatives of your firm and the FDA. The purpose of the meeting was to discuss the development plan for cortexolone 17-α propionate cream, 1%. Your premeeting briefing package dated December 22, 2014, provides background questions for discussion.

We acknowledge the email on January 23, 2015, 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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL RESPONSES

Meeting Type:	Type B
Meeting Category:	End of Phase 2 Meeting
Meeting Date and Time:	January 28, 2015; 11:00am
Meeting Location:	Building 22, Room 1313
Application Number:	IND 112137
Product Name:	cortexolone 17-α propionate cream, 1%
Proposed Indication:	Topical treatment of acne vulgaris in subject 12 years of age and older
Sponsor Name:	Cosmo Dermatos Srl

Introductory Comment:

This material includes the Agency's final responses to the questions submitted for your meeting scheduled for January 28, 2015, at 11:00am in Building 22, Room 1313, between Cosmo Dermatos Srl 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 and/or changing the format of the meeting (e.g., from face-to-face to telecon).

You conveyed to Dawn Williams via email on January 23, 2015 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.

MEETING OBJECTIVE:
To discuss the development program for cortexolone 17-α propionate cream, 1%

Regulatory Correspondence

We have had the following teleconference with you:
- August 10, 2011 Pre-IND

We have sent the following correspondences:

- February 26, 2014 Advice
- January 8, 2014 Special Protocol Agreement (carcinogenicity)
- February 1, 2013 Advice
- August 1, 2013 Advice
- May 30, 2012 Study May Proceed
- February 16, 2012 Information Request

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Does the Agency agree that the drug substance specifications, test parameters, stability program, and acceptance criteria are appropriate and adequate to support the Phase 3 program and NDA submission?

Response:
The tests proposed in the drug substance specification and stability program appear reasonable for Phase 3 program and NDA submission. Acceptability of the acceptance criteria of the tests and retest period of the drug substance will be determined during NDA review.

Question 2:
Does the Agency agree that the Drug Substance impurities above ICH Q3a(r2) qualification threshold have been qualified by use in several nonclinical and clinical studies?

Response:
Your proposed acceptance criteria for the impurities in the drug substance specification appear reasonable at this time. However, the acceptance of a limit for an impurity is determined in the NDA review. You can present your proposed limit with justification in the NDA for review.

Question 3:
Does the Agency agree that the Drug Substance starting materials specifications are adequate to support the Phase 3 program and NDA submission?

Response:
The specification tests appear reasonable. Acceptability of the acceptance criteria of the tests in the specification will be determined during NDA review. A second identification test such as an infrared spectrum should be included in the specification of the drug substance starting material.

Question 4:
Does the Agency agree that the drug product release specifications, test methods, parameters and acceptance criteria are appropriate and adequate to support the Phase 3 program and NDA submission?

Response:
The tests proposed in the drug product **shelf life** specification appear reasonable for Phase 3 program and NDA submission. Acceptability of the acceptance criteria of all the tests will be determined during NDA review. The following additional tests should be included in the drug product specification (**shelf life**): test of uniformity in containers and test of particle size of the drug substance in the cream if the drug is not solubilized in the cream. Additionally, the following tests should be kept in the **shelf life** specification: package weight loss, evaluation of phase separation, microscopic evaluation and package integrity tests.

Question 5:
Does the Agency agree that the Drug Product impurity levels above ICH Q3b(r2) qualification threshold have been adequately qualified to the proposed specification limits via exposure in nonclinical and clinical studies?

Response:
Your proposed acceptance criteria for the impurities in the drug product specification appear reasonable at this time. However, the acceptance of a limit for an impurity is determined in the NDA review. You can present your proposed limit with justification in the NDA for review.

Question 6:
Does the Agency concur with Sponsor's proposed Stability Program to support shelf life determination of CB-03-01 cream as suitable for NDA submission?

Response:
The proposed stability program to support shelf life determination of CB-03-01 cream appears reasonable for NDA submission. However, please be reminded that a bridging study may be necessary if the formulation, manufacturing process, or manufacturing site of the clinical batches used in the pivotal clinical trials is different from that of the commercial batches. You may consult SUPAC-SS for bridging study examples. Additionally, orientation of the tubes of the stability samples needs to be considered during stability studies.

Pharmacology/Toxicology

Question 7:
Does the Agency agree that the completed and planned studies in the nonclinical program are adequate to support the Phase 3 program and NDA submission?

Response:
In principle we agree that the completed and planned studies (Segment III reproductive toxicity and dermal carcinogenicity) are adequate to support the Phase 3 program and NDA submission. However, the final decision will be taken after review of full reports of planned studies.

Question 8:
Does the Agency agree that a request to waive the 9 month CB-03-01 cream minipig study is acceptable?

Response:
Decision will be taken after review of supporting scientific rationale (s) provided with request for a waiver from the 9-month minipig study.

Question 9:
Does the Agency agree that a re-submission of the protocol to the CAC is not required and that Cosmo can initiate the 2-year dermal carcinogenicity study in rats based on the guidance provided in November 2013?

Response:
Yes we agree.

Question 10:
Does the Agency agree that the two nonclinical studies conducted on cortexolone 21-propionate are adequate to qualify this impurity in CB-03-01 cream at levels up to (b)(4)%?

Response:
Such level (b)(4)%) in a drug product is definitely high. Furthermore, the impurity specification is determined during the NDA review.

Question 11:
Does the Agency agree that these pharmacokinetic data are sufficient to support the NDA and no additional ADME studies are needed?

Response:
Yes we agree.

Question 12:
Does the Agency agree that these data are adequate to waive the phototoxicity study?

Response:
Because, 290-700nm scan of drug and inactive ingredients did not reveal absorption of light, a phototoxicity study is not required.

Clinical/Biostatistics

Question 13:
Does the Agency agree with the targeted patient population as defined in the protocol synopsis and as delineated in the inclusion/exclusion criteria?

Response:
You propose principal entry criteria as follows:

- Male and female subjects 12 years of age and older with facial acne vulgaris
- IGA: score 3 - 4
- 30-75 inflammatory lesions

- 30-100 non-inflammatory lesions

The entry criteria, IGA score 3-4, 30-75 inflammatory lesions, 30-100 non-inflammatory lesions are acceptable.

Acne vulgaris is increasing in prevalence in younger children. Its development is strongly linked to the onset of puberty (ref 1). A total of 10% of US girls are menstruating by age 11(ref 2). The age of pubertal onset has been falling for boys and girls over the past several decades (ref 3). According to the National Ambulatory Medical Care Survey, between 1993 and 2009 there were a total of 55 million estimated visits for patients age 18 years and younger with a diagnosis of acne, of these, 4.8% or 2.6 million were for preadolescent acne, ages 7 to 11 years (ref 1). The above information suggests that there are sufficient numbers of patients with acne in the age group less than 12 years and therefore you should include subjects younger than 12 years of age (e.g. 9 years old) in your clinical trial (unless there is a safety issue). See response to question 18.

You propose exclusion of subjects who have the need or plan to be exposed to artificial tanning devices or excessive sunlight during the trial. However, you are requesting a waiver for study of photoxicity and photoallergenicity based on a lack of absorption of light in the 290 to 700 nm range. Clarify your rationale for excluding these subjects.

References:
Davis S A, et al. 2013. Treatment of Preadolescent Acne in the United States: An Analysis of Nationally Representative Data. *Pediatric Dermatology*. 30 (6): 680-694.

Chumlea W C, et al. 2003. Age at Menarche and racial Comparisons in US Girls. *Pediatrics*. 111(1):110-113.

Goldberg J L, et al. 2011. Changing Age of Acne Vulgaris Visits: Another Sign of Earlier Puberty? *Pediatric Dermatology*. 28 (6):645-648.

Question 14:
Does the Agency agree with the co-primary and secondary endpoints for assessing efficacy in the Phase 3 clinical studies?

Response:
In addition to the IGA success [defined as a score of "Clear" or "almost Clear" (IGA score of 0 or 1) AND at least a two-grade improvement in IGA compared to Baseline], you proposed an absolute change in total lesion count as a co-primary endpoint. However, for the indication of *acne vulgaris*, the Agency recommends that absolute changes in inflammatory AND non-inflammatory lesion counts from baseline to Week 12 as well as the IGA success at Week 12 be considered as co-primary endpoints. Consequently, Phase 3 trials should be powered for the changes in lesion counts as well as for the IGA endpoint. Please note that facial acne lesion counts should include lesions on the nose.

For the secondary endpoints, as you proposed the percent changes of inflammatory as well as noninflammatory lesion as secondary endpoints, the percent change of total lesion count might not provide additional information meaningful for labeling.

Note that secondary endpoints intended for labeling should be clinically relevant, limited in number, and adjusted for multiplicity.

Question 15:
Does the Agency agree with the safety endpoints in the Phase 3 clinical studies?

Response:
In general, your proposed safety monitoring, which includes adverse events, local skin reactions, and electrocardiograms, is acceptable.

Question 16:
Does the Agency agree with the proposed statistical plan as outlined in the Phase 3 protocol synopsis?

Response:
Your Phase 2 trial findings do not appear to show a dose-response relationship. Further, your Phase 2 results for the changes in lesion counts and the IGA success are not consistent. You are taking the risk of underpowering future Phase 3 trials based on inconclusive Phase 2 results. It should be noted that, for the selected dose of CB-03-01, 1% BID, the treatment effect for the IGA endpoint was 6% which was based on 6 IGA treatment successes for the CB-03-01, 1% arm (N=70) and 2 IGA treatment successes for the vehicle arm (N=75).

When you subset your data to include the more severe subjects (i.e., subjects with IGA of 3 or 4, 30-75 inflammatory lesions and 30-100 noninflammatory lesions at baseline), you greatly reduced the number of subjects in each arm from 72 subjects to 24 and 22 subjects for the CB-03-01, 1% BID and vehicle arm, respectively. Furthermore, your planned sample size calculation for your Phase 3 trials were based on subgroup analyses using the "continuity-corrected" IGA success rates as well as the least square means from the ANCOVA model. It is not clear whether the treatment effect estimates based on such small sample size and from such modeling and assumptions would be reliable to be used for calculating the sample size for Phase 3 trials. Consequently, you are taking a great risk of underpowering your Phase 3 trials due to the unreliability of the treatment effect estimates.

For your Phase 3 trials, as you submitted a protocol synopsis, it would be difficult to agree with your proposed statistical plan. For detailed comments, submit protocols as well as the Statistical Analysis Plans.

Question 17:
Does the Agency agree that the anticipated extent of patient exposure to the drug product will be adequate to support the safety requirement for an NDA on this formulation?

Response:

We acknowledge your statement that upon completion of the clinical program that over 1400 subjects will have been treated with CB-03-01 cream for the intended dermatological indication, acne vulgaris. We also acknowledge your planned 12 month trial of facial acne vulgaris, including 300 subjects followed for 6 months and 100 subjects for 12 months. In general your proposal is acceptable.

Question 18:
Does the Agency agree that the overall proposed clinical program, subject to data review, is adequate to support an NDA submission?

Response:
Generally, the overall proposed clinical program, subject to data review, appears acceptable. To support an indication of treatment of acne vulgaris in patients 9 years of age and older, you will need to conduct a PK/HPA axis suppression trial under maximal use conditions in subjects down to 9 years of age. You may consider evaluating systemic safety (e.g. HPA axis suppression under maximal use conditions) in younger subjects prior to conducting your Phase 3 trials.

Prior to NDA submission, you should conduct a QT/QTc study to evaluate the potential for QT prolongation or submit a formal request for waiver for Agency review.

We reiterate our recommendation conveyed at the pre-IND meeting on August 10, 2011 that you should consider conducting VCA (vasoconstrictor assay) study to determine the potency classification of your product.

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. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is

waived or deferred.

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.

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

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. 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.

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

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 (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

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/s/

KENDALL A MARCUS
02/17/2015