CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761306Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 119866

MEETING PRELIMINARY COMMENTS

Eli Lilly and Company
Attention: Janelle Erickson, PhD
Senior Director, Global Regulatory Affairs-North America
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Erickson:

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

We also refer to your April 8, 2022, correspondence, requesting a meeting to discuss your plan for submitting a Biologic License Application (BLA) for the treatment of adolescent (12 years to less than 18 years weighing ≥40 kg) and adult patients with moderate-to-severe atopic dermatitis.

Our preliminary responses to your meeting questions are enclosed.

You should provide an 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 301-796-2581.

Sincerely,

{See appended electronic signature page}

Qianyiren Song, PharmD
Regulatory Project Manager
Division of Regulatory Operation for
Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: June 13, 2022; 11:30 a.m. – 12:30 p.m. EST
Meeting Location: Teleconference

Application Number: IND 119866
Product Name: lebrikizumab injection

Proposed Indication: Treatment of adolescent (12 years to 18 years who weigh at least 40 kg) and adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids.

Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 351(a) of the Public Health Service Act

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 June 13, 2022, 11:30 – 12:30 P.M. EDT, via teleconference between Eli Lilly and Company and the Division of Dermatology and Dentistry. 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 me 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

The meeting objectives are to confirm alignment on the studies and table of contents that will be included in the BLA for moderate-to-severe atopic dermatitis and the proposed clinical data package supports the BLA submission, align on the (b) (4) core labeling claims, align on the proposed minimal clinically importance difference (MCID) definition for the (b) (4), discuss the strategy for a (b) (4) recommended

maintenance dose, and discuss the inclusion of the vaccine study at the time of (b) (4) .

Regulatory History:
We have had the following meetings with you:

- October 23, 2020 – Type C CMC meeting (cancelled after receipt of preliminary comments)
- June 19, 2019 – Type B End-of-Phase 2 meeting
- November 8, 2016 – Type C Guidance meeting
- April 13, 2016 – Type C Guidance meeting
- May 28, 2014 – Type C Guidance meeting
- December 11, 2013 – Type B Pre-IND Meeting

We have sent the following correspondences:

- March 25, 2021 - Proprietary Name Conditionally Accepted
- October 21, 2021 - Pediatric Study Plan - Amended Agreement
- January 6, 2021 – Advice
- August 19, 2020 – Change of Sponsor
- May 27, 2020 – Advice
- March 27, 2020 – Advice
- February 25, 2020 – Advice
- December 3, 2019 - Pediatric Study Plan - Initial Agreement
- August 13, 2019 - Pediatric Study Plan – Written Response
- August 13, 2019 – Advice
- July 31, 2019 – Deny Breakthrough Therapy Designation
- January 25, 2017 – Pediatric Study Plan – Written Response
- August 31, 2016 – Deny Breakthrough Therapy Designation
- July 8, 2015 – Advice
- June 24, 2015 – Institutional Review Board (IRB) Waiver Granted
- December 18, 2014 – Acknowledge IND

2.0 DISCUSSION

Question 1:
Does FDA have any comments or questions about the content and organization of the TOC?

FDA Response to Question 1:
From a technical perspective (and not content related), all sections proposed in the Table of Contents (Appendix 1) are acceptable.

Question 2:
Does FDA have any comments on the proposed clinical data package to support the BLA?

FDA Response to Question 2:
You are planning to include data from 8 studies in subjects with moderate-to-severe atopic dermatitis (AD) in the BLA:

- 5 phase 3 studies conducted globally:
  - ADvocate 1and ADvocate 2 (monotherapy studies)
  - ADhere (topical corticosteroids combination study)
  - ADore (adolescents)
  - ADjoin (long-term study that enrolled subjects from the other phase 3 studies and vaccine study, ADopt-VA; direct enrollment was also allowed).
- 3 supportive phase 2 studies conducted in the US:
  - J2T-DM-KGAF
  - TREBLE
  - ARBAN

Your proposed clinical data package appears adequate for filing.

We agree with your proposal to submit Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets for the Phase 2 and Phase 3 trials in subject with atopic dermatitis. We also agree with your proposal to submit the programs used for the primary and major secondary efficacy analyses and the programs used to produce any analyses proposed to be included in the labeling. Also, include the programs used to conduct the supportive and sensitivity analyses for the primary and major secondary efficacy endpoints. In addition, include the programs used to conduct the maintenance analyses and the programs used to implement the multiple imputation (MI) approaches. The programs should be self-contained and executable with the datasets submitted in the BLA.

For ADvocate 2, ADhere, and ADjoin, you propose to exclude one investigator site that participated in these (b) (4) trials (i.e., 5042 in ADvocate 2, 6006 in ADhere, (b) (4)) from the primary analysis population for the efficacy and safety analyses. You stated that “a directed site audit identified that, at one study site, some or all of the study participants did not meet the eligibility criterion of having moderate-to-severe AD, and associated data were unreliable.” Include the data from this investigator site in the BLA submission. Safety data from all exposed subjects should be submitted to the BLA. In addition, submit your site audit with discussion regarding the unreliability of the data.

We also have the following general comments regarding analysis datasets:

a) Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. Include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

b) The analysis dataset documentation (Define.xml) should include adequate 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. Submit corresponding Define.pdf files in addition to the Define.xml files.

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

Question 3:
Does FDA agree that the planned systematic evaluation of safety data proposed in Section 7.3 and further described in the PSAP Version 3 (Appendix 5) will support a substantive review? If not, what additional analyses would FDA recommend?

FDA Response to Question 3:
The planned evaluation of safety data will support substantive review (analysis sets presented in Table 7.2 of the briefing package). We note that on p. 43, you state "(b) (4)" All safety findings should be discussed in the Summary of Clinical Safety. (b) (4) you may also include your assessment on which of those findings you consider are or are not clinically relevant.

In addition to deaths, serious adverse events, discontinuations due to adverse events, and pregnancy, we agree with inclusion of narratives for and discussion of subjects who experience the following notable events:

- Conjunctivitis
  - Notable events: severe conjunctivitis and keratitis
- Infections, including Herpes Infection, and Relevant Parasitic (Helminth) Infections
  - Notable events: severe infections, including severe opportunistic infections
- Eosinophilia and Eosinophilic-Related Disorders
- Hepatic Safety
- Hypersensitivity Reactions
- Injection site reactions

- Malignancies
  - Notable events: malignancies excluding non-melanoma skin cancer
- Suicide/Self-Injury
- Atopic Dermatitis Exacerbation.

Table APP.1.2 in the PSAP summarizes the data to be included in each of the treatment groups for the AD Mono/TCS Weeks 0-52/56 pool. It is clear from the table that the exposure time will be based on the underline portions of the treatment sequences. Confirm that only the safety signals/data from the underline portions will be included.

Question 4:
Does FDA agree that the planned analyses support review of the core labeling claims described above, that is, improvement in measures of (b) (4), improvement in itch severity, use with or without TCS, and (b) (4) for inclusion in labeling? If not, what additional information does the FDA recommend for inclusion in the BLA?

FDA Response to Question 4:
You state that the "following claims are of highest importance to patients and prescribers" (p. 11):

a) (b) (4) improvements on the 5-point IGA (investigator global assessment) scale and the EASI (Eczema area and severity index).

b) significantly improved itch severity as measured by the Pruritus NRS (numerical rating scale)

c) may be used with or without topical corticosteroids (TCS)

d) (b) (4)

Final labeling content will be based on review of the data. However, from the information presented in the briefing package, we have the following comments:

- (b) (4)

  Presentation of statistically significant improvements for the following would be acceptable to include in the labeling. (Note: "patients" would be changed to "subjects"):

- The primary endpoint: "Proportion of patients achieving IGA [0,1] with a 2-point or more improvement from baseline at Week 16" and

- the major secondary endpoints: "Proportion of patients achieving EASI 75 at Week 16" and "Proportion of patients achieving EASI 90 at Week 16 EASI."

- "Proportion of patients with a Pruritus NRS of 4 points or more at Baseline who achieve a 4-point or more reduction from Baseline to Week 16" was also a major secondary endpoint. Presentation of statistically significant improvements for this endpoint (as measured by the 11-point Pruritus NRS) would be acceptable for the labeling.

- Labeling for use of lebrikizumab with or without topical corticosteroids would be acceptable for the labeling, if supported by the data.

- (b) (4)

The primary estimand specifies using a composite strategy to handle intercurrent events of rescue medication use and treatment discontinuation due to lack of efficacy. For intercurrent events of treatment discontinuation due to any reason other than lack of efficacy, the primary estimand specifies using a hypothetical strategy. Include an additional estimand where intercurrent events of rescue medication use and treatment discontinuation due to lack of efficacy and adverse events are handled using the composite strategy and intercurrent events of treatment discontinuation for any other reason are handled using the treatment policy strategy. For each of the Phase 3 trials (ADvocate 1, ADvocate 2, and ADhere), include analysis of the primary and major secondary efficacy endpoints using this additional estimand.

Clarify whether you used remote/virtual visits to conduct efficacy assessments (e.g., IGA and EASI) due to the COVID-19 pandemic. For establishing efficacy claims, the main analysis should be based on in-person visits. However, you may conduct supportive/exploratory analyses that includes efficacy data collected via remote/virtual visits. In your BLA, provide the number of subjects who had missing visits due to the COVID-19 pandemic by treatment group and visit/timepoint for each Phase 3 trial. In your analysis datasets, include a flag that identifies the visits that are missing due to the COVID-19 pandemic along with a variable that contains the reasons for missing the visits (e.g., COVID-19 diagnosis, center closed, subject decision, etc.) when applicable.

Question 5:

(b) (4)

FDA Response to Question 5:

(b) (4)

Also, see the response to Question 4.

Question 6:

Does FDA agree that the proposed strategy with regard to the recommended maintenance dose would be adequately supported by the planned analyses? If not, what other analyses would be required to support this approach?

FDA Response to Question 6:

To assess maintenance and durability of response in the phase 3 monotherapy trials ADvocate 1 and ADvocate 2, subjects originally randomized to lebrikizumab who were responders at Week 16 (defined as having an IGA score of 0 or 1 or EASI 75) were re-randomized to an additional 36 weeks of either a maintenance dose of lebrikizumab 250 mg every 2 weeks (Q2W), lebrikizumab 250 mg every 4 weeks (Q4W), or placebo (PBO).

Efficacy Results of Lebrikizumab for Re-Randomized Lebrikizumab Responders at Week 52 in ADvocate 1; Maintenance Primary Population (Sponsor Table 6.4.)

	Monotherapy Studies		
	ADvocate1		
Induction Period	LEB 250 mg Q2W Responders		
Maintenance Period	**Withdrawal (PBO)**	**LEB 250 mg Q4W**	**LEB 250 mg Q2W**
	N=32	**N=63**	**N=62**
Number of participants who were IGA of 0 or 1 Responders at Week 16[a]	22	45	45
IGA of 0 or 1[a] at Week 52, n (%)	10 (46.5)	33 (74.2)	34 (75.8)
Number of participants who were EASI 75 Responders at Week 16	30	62	61
EASI 75 at Week 52, n (%)	18 (61.3)	49 (79.2)	48 (79.2)

Based on the outcomes at Week 52, it is unclear why (b) (4) Finally, the maintenance dosing did not evaluate subjects from ADhere who were treated with concomitant TCS and you did not discuss how the maintenance dosing regimens apply to TCS use.

Question 7:

(b) (4)

FDA Response to Question 7:

(b) (4)

We do not agree with this approach. The application should be complete at the time of submission.

Additional DMEPA comments:
We are currently reviewing your Use-related risk analysis (URRA) Comparative analysis (CA) submitted November 9, 2021, and will provide written comments upon completion of our review. Your meeting package request states "The Human Factors validation study plan is in development to support the atopic dermatitis indication." Submit the Human Factors Study protocol to your IND for our review and feedback.

The human factors validation study protocol should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

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

Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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

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

since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.*

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

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h3 and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

[3] https://www.fda.gov/media/84223/download
[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[5] https://www.fda.gov/media/85061/download

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

/s/

SHARI L TARGUM
06/09/2022 12:21:32 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND	119866 SDN 100
Request Receipt Date	June 07, 2019
Product	lebrikizumab
Indication	For the treatment moderate-to-severe atopic dermatitis (AD) in adults and adolescent patients 12 years of age and older
Drug Class/Mechanism of Action	Interleukin-13 receptor alpha anatagonist
Sponsor	Demira Inc.
ODE/Division	ODE III/Division of Dermatology and Dental Products
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	Tuesday, August 06, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescent patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☐ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☒ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☒

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

In support of the Breakthrough Therapy Designation (BTD) request, the sponsor presented results from their Phase 2 dose-ranging trial (DRM06-AD01); however, it is not clear how subjects that received rescue medication were treated in the efficacy results. Subjects that received rescue medication should be imputed as failures/non-responders in the efficacy results. If this was not done, then the sponsor needs to submit the results (IGA success [0 or 1 with 2-grade improvement], EASI-75, EASI-90, and ≥4-point improvement from baseline on pruritus NRS at Week 16) with these subjects imputed as failures/non-responders. In addition, for each treatment group, the sponsor should provide the proportion of subjects that received rescue medication. We also note that the efficacy results should be based on the intent-to-treat (ITT) population (i.e., all randomized subjects). We recommend that the missing data for the requested efficacy results be imputed using two approaches: (1) Markov Chain Monte Carlo multiple imputation (i.e., method specified in the protocol) and (2) non-responder imputation. For both approaches, subjects who received rescue medication are imputed as non-responders regardless of whether they have missing data.

For comparative (b) (4) safety data, the sponsor referenced data from the (b) (4) pivotal trials that was published by investigators who participated in those trials (b) (4) The Agency did not rely on those published safety analyses for licensure of (b) (4) Additionally, the sponsor used a cut-point of (b) (4)% for inclusion of adverse events in the sponsor's comparison of "key safety data"; the (b) (4) label presents adverse reactions that occurred in (b) (4)-treated subjects.

Ideally, preliminary clinical evidence indicating that lebrikizumab may demonstrate substantial improvement over (b) (4) would be derived from a clinical study that compares the two products.

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☒

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

12. Division's recommendation and rationale (pre-MPC review):

☐ GRANT:

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☒DENY:

Provide brief summary of rationale for denial:

We have reviewed the request and while we have determined that treatment of moderate-to-severe atopic dermatitis meets the criteria for a serious or life-threatening disease or condition, additional information and data is needed to determine whether the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. See #5 in Section I for details on the needed information and data.

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☐ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

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/

BRENDA CARR
07/23/2019 07:43:26 AM

SNEZANA TRAJKOVIC
07/23/2019 09:33:25 AM

KENDALL A MARCUS
07/23/2019 09:36:57 AM

IND 119866

MEETING MINUTES

Dermira, Inc.
Attention: Drew Badger, PhD, DABT
Vice President, Regulatory Affairs
275 Middlefield Road
Suite 150
Menlo Park, CA 94025

Dear Dr. Badger:

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

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2019. The purpose of the meeting was to provide guidance on the design and adequacy of the proposed Phase 3 clinical development program to support submission of a BLA for lebrikizumab for the treatment of moderate-to-severe atopic dermatitis in patients 12 years and older.

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

If you have any questions, call Barbara Gould, Chief, Regulatory Project Manager at 301-796-4224.

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
- Sponsor's Agenda

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: June 19, 2019; 9:00 a.m. – 10:00 a.m.
Meeting Location: White Oak Campus, Building 32, Room 1309

Application Number: IND 119866
Product Name: lebrikizumab

Proposed Indication: For the treatment moderate-to-severe atopic dermatitis (AD) in adults and adolescent patients 12 years of age and older.
Sponsor Name: Dermira, Inc.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Jennifer Harmon, PharmD

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) III
Soo Hyeon Shin, PharmD, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Jennifer Swisher, PhD, Chemistry, Control and Manufacturing (CMC) Team Lead
Meng-Jung Chiang, PhD, CMC Reviewer
Youwei Bi, PhD, Visiting Associate, Division of Project Management
Jennifer Harmon, PharmD, Regulatory Health Project Manager, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Jordan Adajar, MS, Manager, Regulatory Affairs
Drew Badger, PhD, DABT, Vice President, Regulatory Affairs
Eugene A. Bauer, MD, Chief Medical Officer
Janice Drew, MPH, Senior Vice President, Clinical & Project Management
Ram Gopalan, PhD, Executive Director, Biostatistics
Luis Peña, Chief Development Officer, Product Development
Dale T. Umetsu, MD, PhD, Vice President, Clinical Development
Wiwik Watanabe, PhD, Senior Director, Technical Product Leader

Lydie Yang, Senior Director, Regulatory Affairs

1.0 BACKGROUND

The purpose of the requested meeting was to seek the Agency's guidance on the design and adequacy of the proposed Phase 3 clinical development program to support submission of a BLA for lebrikizumab single injection dosage forms (2 mL PFS-NSD and 2 mL AI) for the treatment of moderate-to-severe atopic dermatitis in patients 12 years and older.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- November 8, 2016 – Guidance
- April 13, 2016 – Guidance
- May 28, 2014 – Guidance
- December 11, 2013 – Pre-IND

We have sent the following correspondences:

- August 31, 2016 – Deny – Breakthrough Therapy Designation
- January 25, 2017 – Initial Pediatric Study Plan – Written Response
- August 4, 2015 – DSUR Revised Due Date Granted
- July 8, 2015 – Advice
- June 24, 2015 – IRB Waiver Granted
- February 5, 2015 – Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 1 (14.5.1) – Product Label Attributes – Phase 3 Primary and Secondary Endpoints
Pending successful outcomes, does FDA agree that the design and planned statistical analyses of the Phase 3 clinical trials, DRM06-AD04, DRM06-AD05 and DRM06-AD06, would support inclusion of the results for the primary and secondary endpoints in the product label?

FDA Response to Question 1 (14.5.1):
Your query pertains to the following endpoints:

- The primary endpoint:
  - the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 and a reduction of ≥ 2 points from baseline at Week 16.

- Key secondary efficacy endpoints assessed at Week 16:
  - the proportion of patients achieving EASI-75,
  - the proportion of patients achieving EASI-90,
  - the proportion of patients with ≥ 4-point reduction in pruritus, using the pruritus numerical rating scale (NRS) (11-point NRS).

These endpoints appear reasonable for consideration for labeling, pending review of the data in the BLA submission. The final content of labeling will be determined during the BLA review cycle.

Question 2 (14.5.2) – Product Label Attributes – Maintenance Dosing

Does FDA agree that the design of the maintenance period (Week 16 through 32) of the monotherapy trials, DRM06-AD04 and DRM06-AD05, is sufficient to support the inclusion of a time-course graph illustrating the maintenance of efficacy in the product label?

FDA Response to Question 2 (14.5.2):

The specific content of labeling in Section 14 will be considered during the BLA review. However, we note that (b) (4) [redacted] See FDA Response to Question 4d (14.2.4.d) for comments regarding the Agency's recommended definition of success and the re-randomization at Week 16.

Question 3 (14.5.3) – Product Label Attributes – Treatment with Concomitant Topical Corticosteroids

Pending successful outcomes, does FDA agree that the design and planned statistical analysis of DRM06-AD06 TCS Combination trial would support label claims related to:

a. Use of lebrikizumab in combination with TCS (in addition to monotherapy claims) in the indicated target population

b. (b) (4) [redacted]

c. (b) (4) [redacted]

FDA Response to Question 3 (14.5.3):

a. Contingent on successful outcomes, the design DRM06-AD06 TCS Combination trial appears adequate to support an indication for use of lebrikizumab with TCS. However, the precise content of labeling is determined during the BLA review.

b. See FDA Response to Question 5 (14.2.5) regarding "(b) (4)" and "(b) (4)"

c. Response to this question will be provided as "Post Meeting Response".

Post Meeting Response to Question 3.c (14.5.3.c):

(b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

2.3. Nonclinical

Question 1 (14.1.1) – Toxicology
Does the FDA agree that the completed toxicology program is adequate to support the proposed initial marketing application for patients 12 years and older with moderate-to-severe atopic dermatitis and future marketing applications for pediatric patients 6 months to < 12 years old (consistent with prior feedback - Type C meeting held 08 on November 2016)?

FDA Response to Question 1 (14.1.1):
We agree that the completed toxicology program is adequate to support the proposed initial marketing application for patients 12 years and older with moderate-to-severe atopic dermatitis and future marketing applications for pediatric patients 6 months to < 12 years old.

We acknowledge that you plan to submit a carcinogenicity risk assessment in your BLA application. This is acceptable and will be reviewed under the BLA.

2.4. Clinical Pharmacology

Question 1 (14.2.1) – Overall Clinical Development Plan
Does FDA agree that the proposed clinical data package appears sufficient to support submission of a BLA for lebrikizumab for the treatment of moderate-to-severe AD in patients 12 years and older (and ≥ 40 kg) used with or without topical corticosteroid (TCS) as described in Proposed Indications (Section 5)?

FDA Response to Question 1 (14.2.1)
It is premature to provide any agreement at this time as the pharmacokinetics of lebrikizumab has not been fully characterized in your development program.

Additional Comments:
For immunogenicity assessment planned in your Phase 3 studies (DRM06-AD04 and DRM06-AD05), we recommend you collect additional ADA sample at Week 4.

Meeting Discussion:
The sponsor will provide information on complete pharmacokinetic (PK) characterization as well as they will also address the effect of disease on PK in the BLA submission.

Question 2 (14.2.2.) – Dose Selection for Phase 3

The proposed initial induction dosage regimen for the Phase 3 clinical trials is 250 mg administered as a 2 mL subcutaneous injection administered every 2 weeks for 16 weeks (250 mg Q2W), with a loading dose of 500 mg each at baseline and at week 2. A dose of 250 mg lebrikizumab Q2W and a dose of 250 mg lebrikizumab every 4 weeks (Q4W) have been selected for the assessment of maintenance dosing in Phase 3.

Does the FDA agree with this proposal?

FDA Response to Question 2 (14.2.2.):

The proposed dosing regimen in your Phase 3 trials appear reasonable based on the efficacy and safety results from the Phase 2, dose-ranging study (DRM06-AD01).

Question 3 (14.2.3) – Inclusion of Adolescents in Phase 3 Trials

Does FDA agree with inclusion of adolescent patients (12 to < 18 years and a body weight ≥ 40 kg) with moderate-to-severe AD in the Phase 3 trials consistent with the iPSP?

FDA Response to Question 3 (14.2.3.):

Inclusion of adolescent patients appear reasonable. The Agency noted that based on Pop-PK simulation, an adolescent patient with a body weight of 54 kg will have 30% higher exposure compared to adult patient weighing 70 kg with the same dose. We recommend you conduct an exposure-safety analysis based on data from study DRM06-AD01 to further illustrate the relationship between exposure and adverse events. You should demonstrate that 30-40% higher exposure in adolescent patients is not expected to have higher risks for adverse events prior to the initiation of Phase 3 trials. Alternatively, you can consider proposing a weight-tiered dosing regimen in adolescent patients to fully match the adult exposure.

Your proposed indication is “Treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescent patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Lebrikizumab can be used with or without topical corticosteroids.” However, enrollment in your clinical trials is not strictly age-based, as you would require that subjects be ≥ 12 years *and* ≥ 40 kg. Your indication should reflect the target population that you intend for your product.

Question 6 (14.2.6.) – Autoinjector Bridging Strategy

The Sponsor understands that the complete data package including human factors, bioequivalence, and clinical data would be necessary to provide definitive feedback; however, based on the proposed set of studies, does the FDA perceive any major deficiencies or concerns with the overall bridging strategy to support the use of the 2 mL AI in addition to the 2 mL PFS-NSD?

FDA Response to Question 6 (14.2.6.):
We acknowledge your plan to conduct a comparative PK study with the PFS-NSD and AI. We note that your Phase 3 studies and long-term safety study is planned with the pre-filled syringe. The results of the comparative PK study might suggest the need for additional studies.

Meeting Discussion:
The Agency clarified that the sponsor might need to address the difference in systemic exposure with additional safety and/or efficacy data if the results of the comparative PK study are outside the no-effect boundary of 80%-125%.

The Agency stated that the human factor study would be helpful.

Question 7 (14.2.7.) – Waiver of Drug-Drug Interaction Study
Does the FDA agree that drug-drug interaction (DDI) studies are not needed for lebrikizumab to be approved for the proposed indication?

FDA Response to Question 7:
We acknowledge your rationale for not proposing DDI studies for lebrikizumab based on in vivo study results reported in Davis et al. (2018). The adequacy of your rationale will be reviewed at the time of your BLA submission.

2.5. Clinical/Biostatistics

Question 1 (14.3.1) – Safety
Does FDA agree that the proposed safety database at the time of BLA submission appears adequate, assuming no new safety signals are detected?

FDA Response to Question 1 (14.3.1):
At the time of BLA submission, you expect the safety database to include exposure data for (numbers are approximate):

- 1450 AD subjects who received any dose of lebrikizumab.
- 400 subjects enrolled in other lebrikizumab trials who had concomitant AD and received at least one dose of lebrikizumab.
- 475 AD subjects treated with the intended lebrikizumab dose, for ≥ 6 months. Additionally, the database will include approximately 12 subjects enrolled in lebrizikumab trials who had concomitant AD and were dosed with lebrikizumab, for ≥ 6 months, at doses ≥ 250 mg Q4W.
- 375 AD patients treated with lebrikizumab, at the intended dose for ≥ 1 year.

From the discussion in the briefing package, the number of AD subjects exposed to each dosing regimen is unclear. For example, in Table 9 you present the number of AD subjects "exposed to proposed dose/regimen of 250 mg Q2W or Q4W" as a single category, without describing the number of subjects exposed to *each* regimen. Information pertaining to the 250 mg Q2W would support 250 mg Q4W regimen; the reverse would not be true.

On submission of the BLA, we recommend a safety database that includes 750 subjects with moderate to severe atopic dermatitis who have received the to-be marketed dose (concentration and frequency) for at least one year, and of the 750 subjects, a minimum of 30% should be between the ages of 12 and 17 years old.

Meeting Discussion:
The sponsor proposed to supplement the planned 150 adolescent subjects by conducting an open-label study in order to attain a safety database containing 250 adolescent subjects who have received the to-be-marketed dose for at least one year.

(b) (4)

Question 2 (14.3.2) – Cardiac Safety and Pressor Effect
Does FDA agree with the Sponsor's plan to collect blood pressure data at clinic visits during the Phase 3 pivotal trials to further characterize the effects of lebrikizumab on blood pressure and that more thorough assessment via Ambulatory Blood Pressure Monitoring is not required?

FDA Response to Question 2 (14.3.2):
This is acceptable.

Question 4 (14.2.4) – Phase 3 Monotherapy Efficacy and Safety Trials
Does FDA agree with the overall design of the two proposed monotherapy Phase 3 efficacy and safety trials (DRM06-AD04 and DRM06-AD05)? Specifically, the Sponsor seeks feedback on:

a. The key inclusion/exclusion criteria defining the patient population to be studied.
b. The proposed primary endpoints and secondary efficacy endpoints intended for product label inclusion.
c. Adequacy of the statistical analyses proposed for the primary and secondary endpoints.
d. The ability of the maintenance study design and data pooling strategy to provide (b) (4) maintenance dose (b) (4) in the product label.

FDA Response to Question 4:

You have provided protocol synopses for your Phase 3 trials (DRM06-AD04 and DRM06-AD05). Additional comments may be conveyed once full protocols with complete statistical analysis plans are submitted for Agency review.

a. You propose to define the target population by the following criteria: atopic dermatitis (AD) for at least one year, an EASI score ≥ 16, an IGA score ≥ 3 and have ≥ 10% BSA of AD involvement. All subjects will have a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable. Your proposed definition of the target population is acceptable.

b. The primary efficacy endpoint is the percentage of patients with an IGA score of 0 or 1 and a ≥ 2-point reduction from Baseline to Week 16.

   Your development program is intended to support a BLA submission in the United States and a Marketing Authorisation Application (MAA) in the European Union (EU). You selected and prioritized your secondary efficacy endpoints to support European Medicines Agency (EMA) requirements to establish efficacy and for additional labeling statements regarding induction and maintenance of treatment response. The secondary endpoints that you propose for inclusion in the label are:

   - Percentage of patients achieving EASI-75 from Baseline to Week 16
   - Percentage of patients achieving EASI-90 from Baseline to Week 16
   - Proportion of patients with ≥4-point reduction from Baseline to Week 16 in Pruritus NRS

   The listed endpoints are acceptable and may be included in labeling depending on statistical outcomes. You propose several secondary endpoints based on change (and percent change) from baseline. We note that a mere change (and percent change) may not translate to a clinically meaningful improvement; consequently, these endpoints may not be appropriate for labeling. The precise content of labeling will be determined during labeling negotiations during the BLA review.

c. The following are statistical comments pertaining to the protocol synopses included in the meeting package:

   - Your proposal to analyze binary efficacy endpoints using the using the Cochran-Mantel-Haenszel (CMH) test adjusted by the randomization strata is acceptable. For continuous endpoints, (b) (4)

(b) (4) the analysis should be based on only data from one timepoint (e.g., Week 16); (b) (4) modeling approaches using all timepoints may be used as supportive analyses.

Meeting Discussion:
The sponsor agreed to conduct the primary analysis for establishing efficacy at one time point (Week 16). Analysis based on repeated measure would be considered as a supportive for those of the primary analysis.

- *To control the Type I error rate for testing multiple efficacy endpoints, you propose using a gatekeeping approach with a required significance level of (b) (4) to test subsequent endpoints. As it appears you plan to use two-sided tests, it is not clear why you are specifying a significance level of (b) (4) instead of 0.05 in your gatekeeping approach. Clarify. We note that your last secondary endpoint includes (b) (4) ; however, this is not taken into consideration in your proposed multiplicity testing strategy. Secondary endpoints intended for labeling should be limited in number, clinically meaningful, and analyzed with appropriate multiplicity control. See FDA Response to Question 4b (14.2.4.b) for comments regarding the proposed secondary endpoints.*

Meeting Discussion:
The sponsor acknowledged (b) (4)

- (b) (4) *Subjects who received rescue medication during the trial should be treated/imputed as non-responders for the efficacy analyses. It is not clear whether this was taken into consideration in the results you provided for the Phase 2 trial (DRM06-AD01), which are being used to select the dose regimen and powering the Phase 3 trials.*

Meeting Discussion:
The sponsor agreed to treat subjects who received rescue medication during the trial as treatment failures in the primary efficacy analysis. For continuous endpoints, these subjects will be imputed using the baseline value.

The sponsor also asked whether it would be acceptable to allow rescue therapy during weeks 4 to14 using mid-potency TCS or calcineurin products. The treatment will be of ≤ 3 consecutive days in duration and not more than total of 5 days within 16-week treatment period. The Agency responded that the proposal may appear reasonable

however, an additional internal discussion will be needed before the decision on this proposal can be made.

d. For the maintenance period, you propose to re-randomize subjects who achieve EASI-75 at Week 16. As the primary efficacy endpoint is success on the IGA (i.e., score of 0 or 1 with at least a 2-point improvement from baseline) at Week 16, we recommend re-randomizing subjects who achieve success on the IGA at Week 16. However, we acknowledge that your clinical development program needs to be designed to satisfy the requirements of multiple regulatory authorities. Therefore, you may also include subjects who only achieve EASI-75 at Week 16 in the re-randomization (subjects who achieve success on IGA and EASI-75 would already be included in the re-randomization as they meet the IGA criterion).

   Descriptive information regarding maintenance of response may be appropriate for labeling. Whether the data from the two Phase 3 trials could be pooled will be dependent on how similar the results are between the two trials.

   You plan to re-randomize subjects who are placebo responders at Week 16 to continue placebo or switch to lebrikizumab. Clarify your rationale and the utility for re-randomizing these subjects.

Meeting Discussion:
The sponsor provided their justification for re-randomizing subjects who are placebo responders at Week 16 (see attached). The Agency stated that their justification appeared reasonable.

Additional Comment:

Given that conjunctivitis, herpes virus infections and zoster, and "eosinophil-associated" adverse events have only been observed in lebrikizumab-treated subjects, we recommend that these events be designated as adverse events of special interest (AESIs) in the Phase 3 program. Additionally, report relevant parasitic infections and infections due to intracellular pathogens as AESIs.

Meeting Discussion:
The sponsor discussed that only mild events of eosinophilia have been observed in the AD program. Based on these observations they proposed that eosinophil-associated adverse events not be considered AESIs. The Agency agreed.

Question 5 (14.2.5.) – Topical Corticosteroid (TCS) Combination Study
Does FDA agree with the overall design of the Phase 3 combination efficacy and safety trial (DRM06-AD06)? Specifically, does FDA agree with:

a. The key inclusion/exclusion criteria defining the patient population to be studied?

b. The proposed primary endpoints and secondary efficacy endpoints, [redacted] (b) (4) (see Section 14.5.3)?

c. Adequacy of the statistical analyses proposed for the primary and secondary endpoints?

d. [redacted] (b) (4) ?

FDA Response to Question 5 (14.2.5):

You have provided a protocol synopsis for your Phase 3 trial (DRM06-AD06). Additional comments may be conveyed once a full protocol with a complete statistical analysis plan is submitted for Agency review.

You will provide mid-potency topical corticosteroids (TCS) and a low-potency TCS will be provided for use in this trial. Subjects will be instructed to use a mid-potency TCS from Baseline and may taper use and stop when disease is controlled (clear or almost clear). Subjects may use low-potency TCS or topical calcineurin inhibitors (TCIs) to treat sensitive skin areas such as the face.

a. The definition of the study population is the same as for the monotherapy trials and is acceptable.

b. In addition to the secondary endpoints to be evaluated in the monotherapy trials, the combination trial will also evaluate the following secondary endpoints:

- Proportion of TCS / TCI-free days through Week 16, calculated as the number of days that a patient used neither TCS/ TCI nor system rescue therapy divided by the number of study days
- [redacted] (b) (4)

Your proposed indication statement is "treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescent patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. *Lebrikizumab can be used with or without topical corticosteroids*" (emphasis added).

It is unclear how inclusion of information pertaining to "[redacted] (b) (4)" or "[redacted] (b) (4)" would meaningfully inform the label, since your proposed indication allows for "as needed" use of TCS (which would be inherently variable), including no use of TCS.

You propose several secondary endpoints based on change (and percent change) from baseline. We note that a mere change (and percent change) may not translate to a clinically meaningful improvement; consequently, these endpoints may not be appropriate for labeling.

c. The following are statistical comments pertaining to the protocol synopsis included in the meeting package:

- Your proposal to analyze binary efficacy endpoints using the using the Cochran-Mantel-Haenszel (CMH) test adjusted by the randomization strata is acceptable. For continuous endpoints, (b) (4) the analysis should be based on only data from one timepoint (e.g., Week 16); (b) (4) modeling approaches using all timepoints may be used as supportive analyses.

- To control the Type I error rate for testing multiple efficacy endpoints, you propose using a gatekeeping approach with a required significance level of (b) (4) to test subsequent endpoints. As it appears you plan to use two-sided tests, it is not clear why you are specifying a significance level of (b) (4) instead of 0.05 in your gatekeeping approach. Clarify. In addition, we note that your list of secondary endpoints includes (b) (4) ; however, this is not taken into consideration in your proposed multiplicity testing strategy. Secondary endpoints intended for labeling should be limited in number, clinically meaningful, and analyzed with appropriate multiplicity control. See FDA Response to Question 5b (14.2.5.b) for comments regarding the proposed secondary endpoints.

- (b) (4) Subjects who received rescue medication during the trial should be treated/imputed as non-responders for the efficacy analyses.

d. Response to this question will be provided as "Post Meeting Response".

See "Post Meeting Response to Question 3.c (14.5.3.c)."

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to

[4] https://www.fda.gov/media/88173/download
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

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

[7] https://www.fda.gov/media/88173/download
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

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).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical*

[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/media/109533/download

Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[12]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to

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

endpoint measures, dose, and/or population)

- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ATTACHMENT

- Sponsor's Agenda

19 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KENDALL A MARCUS
07/09/2019 08:45:35 AM