CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761391Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 117122

MEETING MINUTES

Galderma Research & Development, LLC
Attention: Amy Campbell
Head of Nemolizumab Regulatory Strategy
2001 Ross Avenue; Suite 1600
Dallas, TX 75201

Dear Ms. Campbell:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 24, 2023. The purpose of the meeting was to discuss the content and format of your proposed BLA submission for the treatment of moderate to severe atopic dermatitis in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies.

A copy of the official minutes of the teleconference 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, Safety Regulatory Project Manager at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH
Acting Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's slides

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	April 24, 2023; 1:30pm-2:30pm
Meeting Format:	Teleconference
Application Number:	IND 117122
Product Name:	nemolizumab
Proposed Indication:	For the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies
Sponsor Name:	Galderma Research & Development, LLC
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Shari Targum, MD
Meeting Recorder:	Dawn Williams, BSN

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Immunology and Inflammation (OII)
Nikolay Nikolav, MD, Deputy Director, OII
Shari Targum, MD, Acting Director, Division of Dermatology and Dentistry (DDD)
Dave Kettl, MD, Clinical Team Leader, DDD
Dawn Williams, BSN, Safety Regulatory Project Manager, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Anand Balakrishnan, PhD, Clinical Pharmacology Reviewer, DIIP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III (DBIII)
Kathleen Fritsch, PhD, Biometric Reviewer, DBIII

SPONSOR ATTENDEES

Christophe Piketty, Global Nemolizumab Program Head
Dario Beltramo, Head of Toxicology
Michael Graeber, Chief Medical Advisor and Head of Medical Expertise
Liliana Ulianov, Senior Medical Expert
Kenny Frazier, Head of Clinical Development
Nathalie Wagner, Head of Clinical Pharmacology
Patricia Fleuranceau Morel, Head of Clinical Safety, Pharmacovigilance Risk Management
Faiz Ahmad, Head of Biometrics
Soo Yeon Cheng, Principal Biostatistician
Regis Schulz, Head of Global Regulatory Affairs

Erik Bjornson, Head of Global Biologics Regulatory Strategy
Amy Campbell, Head of Nemolizumab Regulatory Strategy

1.0 BACKGROUND

We have had the following meetings with you:

- September 26, 2022; Guidance
- September 8, 2021; Guidance
- December 1, 2020; Guidance
- May 20, 2020; End of Phase 2
- January 27, 2020; Guidance
- March 20, 2019; End of Phase 2
- September 12, 2018; Guidance
- March 7, 2018; Stalled Development Pediatric Study Plan
- March 13, 2017; Guidance
- July 2, 2014; Guidance
- February 20, 2013; Guidance

We have sent the following correspondences:

- August 9, 2022; 1572 Signature Waiver Granted
- August 2, 2021; Initial Pediatric Study Plan- Amended Agreement
- May 7, 2021; Initial Pediatric Study Plan- Written Response
- October 13, 2020; Advice
- November 27, 2019; Advice
- August 22, 2019; Initial Pediatric Study Plan- Initial Agreement
- May 31, 2019; Initial Pediatric Study Plan- Written Response
- July 6, 2017; Initial Pediatric Study Plan- No Agreement
- August 5, 2014; Initial Pediatric Study Plan- Written Response
- November 22, 2013; Study May Proceed

2.0 DISCUSSION

2.1. Nonclinical

Question 1:
Does the Agency agree that the nonclinical package for the nemolizumab program is adequate to support a BLA filing for the AD indication?

FDA Response to Question 1:
Yes, we agree that your nonclinical program appears reasonable to support a BLA submission for the AD indication.

Question 2:

Does the Agency agree that the Sponsor has fulfilled the carcinogenicity assessment requirements to support a BLA filing and Agency review for nemolizumab for the treatment of AD? Specifically, does the Agency have any comments regarding the Carcinogenicity Risk Assessment Document (CAD) submitted as a part of this briefing document?

FDA Response to Question 2:
Yes, we agree that your updated carcinogenicity risk assessment document appears appropriate to support a BLA filing and Agency review for the AD indication. In addition, we note that this document also appears appropriate to support a BLA filing for the PN indication.

2.2. Clinical Pharmacology

Question 3:
The Sponsor intends to request a waiver from requirement to conduct a thorough QT/QTc study for nemolizumab to the interdisciplinary Review Team for Cardiac Safety Studies.

a) Does the Agency agree with the proposed timing of the waiver request and that this will not impact the review of the proposed BLA?
b) Does the Agency have any additional requests for the QT/QTc evaluation and review?

FDA Response to Question 3:
You have proposed to submit a waiver request for the conduct of thorough QT/QTc study to the IND by mid-May 2023 and you have also indicated that you will submit the waiver request under the BLA in module 1.

Your proposal appears reasonable. If you plan to submit separate BLAs for the AD and PN indication, then you would need to submit a separate thorough QT/QTc waiver request to each of the applications.

Question 4:
Does the Agency agree on the content and format of Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods?

FDA Response to Question 4:
The proposed content and format of the Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods appears reasonable.

We have the following comments for your consideration:

- We note that you have utilized multiple assays for the quantification of nemolizumab throughout your development program. Provide a summary of the cross-validations across the various assays conducted to support the AD indication.

- We note that the formulation/presentation used in the pivotal study is different from the to-be-marketed presentation. As a result, you will need to establish a clinical bridge between the two presentations. Provide results from any clinical studies conducted to support the clinical bridge along with the associated datasets in SAS transport (XPT) format in the BLA. This will be a review issue.

Meeting Discussion:
The sponsor proposed to provide the requested information in the original BLA submission. The Agency acknowledged their proposal.

Question 5:
Does the Agency agree that the content and format of the Module 2.7.2 Summary of Clinical Pharmacology Studies is sufficient to support submission of a BLA?

FDA Response to Question 5:
The proposed content and format of the Module 2.7.2 Summary of Clinical Pharmacology Studies appears reasonable.

Question 6:
Does the Agency agree on the proposed content, format and Common Technical Document (CTD) location of the ISI? Specifically,

- Location of ISI in Module 5.3.5.3
- Inclusion of immunogenicity risk assessment for nemolizumab
- Detailed descriptions of ADA/NAb assay methods and validated assay performance applied for analysis of samples from all clinical studies
- Descriptive outputs of relationship of ADA/NAb signals to drug exposure, efficacy and safety for pivotal clinical studies
- Summary of ADA/NAb response dynamics in Phase 1 and Phase 2 studies

FDA Response to Question 6:
The proposed content and format of the content, format and location of the ISI appears reasonable.

We have the following comments for your consideration regarding the analysis of immunogenicity data:

- For the evaluation of the ADA impact on PK, we recommend that you compare PK data using between-subject comparisons (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive).
- We also encourage you to include subjects ADA status and titer as time-varying covariates in the population PK analysis on an exploratory basis to evaluate the impact of ADA on your drug's PK.

- For the evaluation of the ADA impact on efficacy, we recommend that you compare changes in efficacy using between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive).

Question 7:
Does the Agency agree that the popPK and PK/PD approaches and the proposed data sets will be sufficient to enable FDA's Pharmacometrics team review?

FDA Response to Question 7:
Your proposal appears reasonable for filing. ADA status and titer should be treated as time-varying covariates in the population PK analysis. In addition, the dose/exposure-response analyses for efficacy (including primary and secondary clinical efficacy endpoints for each specific indication) and safety for adverse events of special interest should also be submitted.

Meeting Discussion:
Your proposed PK/PD and ER analysis appears reasonable. The sponsor proposed to conduct ER safety analysis on selected adverse events with incidence of more than 1%. The Agency responded that the sponsor's proposal is reasonable, and the adequacy will be a review issue.

2.3. Clinical

Question 8:
Does the Agency agree that the clinical studies planned for inclusion in the BLA submission are adequate for the evaluation of safety and efficacy of nemolizumab and supportive of the intended indication?

FDA Response to Question 8:
The proposed content of the application appears adequate for filing.

Question 9:
Does the Agency agree that the strategy for pooling data from the subjects who experienced response (i.e. IGA 0 or 1 and/or EASI-75) at week 16 (i.e., end of the treatment phase and randomization of responders to the maintenance phase) from the two pivotal Phase 3 studies (SPR.118161 and SPR.118169) in atopic dermatitis supports the Agency's evaluation of the two maintenance phase dose regimens (i.e., Q4W or Q8W following completion of the 16-week treatment period) in the BLA submission?

FDA Response to Question 9:
Each clinical study report should include the protocol-specified analyses for both the treatment and maintenance stages of the trials. It is acceptable to calculate estimates from integrated analyses across the two Phase 3 trials to increase

precision in addition to the individual analyses, however, the primary assessment of the findings for the maintenance phase of the two trials will be from the individual study findings. We recommend that appropriate statistical approaches for integrating data across these trials should be considered to account for differences in trial design.

Meeting Discussion:
The approach presented in the sponsor's supplemental slides (slide #5) is acceptable.

Question 10:
Does the Agency agree with the Sponsor's proposal to include the narrative portion of the ISE in Module 2.7.3?

FDA Response to Question 10:
While this proposal is generally acceptable, see the response to question 3 from the September 26, 2022, meeting discussion as well as the Agency Guidance for Industry: *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

2.4. Biostatistics

Question 11:
Does the Agency agree that the content and format of the study datasets proposed are sufficient to support the filing and review of the AD BLA?

FDA Response to Question 11:
We agree with your proposal to submit CDISC-compliant study datasets in accordance with the current Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in SAS transport (xpt) format.

Submit datasets for the Phase 2 proof-of-concept trial SPR.114322, along with the datasets for the Phase 3 trials.

We concur with your approach to include statistical programs for imputation methods and any non-standard analyses. The submitted programs should support the primary and key secondary endpoints for the Phase 3 trials.

Include an annotated case report form. If any data is collected via electronic data capture rather than directly on the CRF, include annotated screen shots of the electronic data capture system.

For each trial, include the final protocol along with any protocol amendments and the statistical analysis plan.

Question 12:
Does the Agency agree with the proposed efficacy analysis for the ISE, as presented in the AD ISE Statistical Analysis Plan (SAP)?

FDA Response to Question 12:
Your proposal to present side-by-side analyses from the Phase 3 trials for the primary and key secondary endpoints and subgroup analyses pooled across the two trials is acceptable.

2.5. Safety

Question 13:
a) Does the Agency agree with the proposed cut-off date of 30 Sep 2022 for the AD Safety Database?
b) Does the Agency agree with the Sponsor's approach to the presentation of accumulated safety data in Module 2.7.4 of the BLA to support the Agency's assessment of nemolizumab in the proposed indication?

FDA Response to Question 13:
a) No, the proposed cutoff date, which predates the planned application submission by a year, or perhaps longer, will present an unnecessarily large amount of data to be reviewed following submission of the safety update, particularly given the complexity and size of the development program. The March 2023 cutoff date proposed for the prurigo nodularis application is more reasonable and more typical for new product applications.

b) The Agency noted that the proposed numbers as outlined in the December 2020 meeting were generally acceptable for filing and the adequacy of the safety evaluation would be a review issue under the BLA.

Meeting Discussion:
The revised sponsor proposal as submitted in the response to the draft meeting comments is acceptable. Our objective is to be able to evaluate data from the initial application to support the Section 6 labeling proposals without extensive re-analysis upon submission of the safety update.

Question 14:
a) Does the Agency agree with the proposed cut-off date of 21 Jul 2023 for the 4-month safety update, which will include new safety information for the ongoing AD LTE study, the completed and ongoing additional studies conducted by the Sponsor and another Sponsor (Maruho) in AD and other indications?
b) Does the Agency agree with the Sponsor's approach to the safety data presented in the 4-month safety update?

FDA Response to Question 14:

a) Yes
b) Yes

2.6. Regulatory

Question 15:
Does the Agency consider the proposed Table of Contents (TOC) and strategy for Modules 1-5 to be adequate to support review of the nemolizumab AD BLA?

FDA Response to Question 15:
From a technical perspective (and not content related), the proposed Table of Contents is acceptable. See Response to question 17 regarding various application scenarios.

Question 16:
Does the Agency agree with the Sponsor's proposed definition of covered clinical studies for the purposes of reporting financial disclosures and summary level clinical site information as a part of BIMO requirements?

FDA Response to Question 16:
Yes, your proposal appears reasonable. Additional discussion regarding BIMO requirements can be found in the Agency guidance, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*.

Question 17:
The Sponsor would like to confirm that the Agency advice from the 26Sep2022 ISS guidance meeting (FDA Minutes Ref. ID 5054766) and the 26Oct2022 BTD guidance meeting (FDA Minutes Ref. ID 5092316) continue to apply should we elect to submit a single BLA submission to support indications for both the treatment of AD and the treatment of PN?

FDA Response to Question 17:
The referenced meeting advice previously provided remains applicable regardless of the type and numbers of applications for the two disparate indications based on our understanding of your development plans to date.

If you choose to submit one application, it appears likely that we would administratively split the different indications and they would be reviewed as separate submissions on different clocks should the application for prurigo nodularis be awarded expedited review. The indication with the later goal date would then become an efficacy supplement to the first action should the initial indication be approved on the expected timeline.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 22, 2023 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 VII. 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. 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 FDA.gov.[1]

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.*[2] 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.[3]

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[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst

females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.*

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

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types**: NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[12]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see FDA.gov.[13]

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 356h16 and the guidance for industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers17. 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.[1]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products,* stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

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

[1] 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
04/25/2023 12:23:30 PM

IND 117122

MEETING MINUTES

Galderma Research and Development, LLC
Attention: Stacie M. Winter
Regulatory Submissions Manager
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Winter:

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

We also refer to the meeting between representatives of your firm and the FDA on March 20, 2019. The purpose of the meeting was to discuss the development program for nemolizumab.

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
- Sponsor's Slides

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: March 20, 2019; 10:30am
Meeting Location: Building 22, Room 1309

Application Number: IND 117122
Product Name: nemolizumab
Indication: For the treatment of moderate-to-severe atopic dermatitis (AD) (b) (4) in patients ≥12 years old, who are inadequately controlled by topical therapies; (b) (4) (b) (4)

Sponsor Name: Galderma Research and Development, LLC

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

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong Wang, PhD, Pharmacology Reviewer, DDDP
Dawn Williams, BSN, Regulatory Project Manager, DDDP
Dennis Bashaw, PhD, Senior Scientific Advisor, Office of Clinical Pharmacology
Chinmay Shukla, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3
Jiang Liu, PhD, Lead Pharmacologist, Division of Pharmacometrics
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biostatistics III (DB III)
Matt Guerra, PhD, Biostatistics Reviewer, DB III
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Yasmin Choudhry, MD, Reviewer, COA
Peter Petrochenko, PhD, Lead Reviewer, General Hospital Devices Branch

SPONSOR ATTENDEES
Michael Graeber, Chief Medical Advisor & Head of Medial Expertise
Zarif Jabbar-Lopez, Medical Expert
Kenny Frazier, Head, Global Prescription Development Research and Development
Mayumi Hori, CMC Regulatory
Shoen Todaka, CMC Regulatory
Elisabeth Rosner, Head of Toxicology
Nathalie Wagner, Senior Clinical Pharmacokinetics Manager
Gerald Pedrassi, Head of CMC Development
Toru Shimuta, Manager CMC Analytical
Bobbi Drais, Head of Global Regulatory Affairs
Stacie Winter, Regulatory Submissions Manager
Christopher Piketty, Global Senior Project Leader
Ted Wagner, Senior Clinical Project Manager
Faiz Ahmad, Head of US Biostatistics
(b) (4) Consultant

1.0 BACKGROUND

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

- October 24, 2018 Final Written Response
- September 12, 2018 Guidance
- March 7, 2018 Stalled Development Pediatric Study Plan
- March 13, 2017 Guidance
- July 2, 2014 Guidance
- February 20, 2013 Pre-IND

We have sent the following correspondences:

- July 6, 2017 Pediatric Study Plan- Initial No Agreement
- August 5, 2014 Pediatric Study Plan- Written Response
- November 22, 2013 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 17:
The Sponsor proposes to include complete information on the device and its constituent parts as part of the BLA submission. Does the Agency agree?

FDA Response to Question 17:
We agree that you should provide complete information for the device constituent of your combination product in your future BLA submission. However, a device

description and design control information should be provided under the IND. Please refer to additional comments (list #s of additional comments) for more infomration. Additional product and device-related CMC information was provided in the Type C meeting held on October 30, 2018.

Additionally, the Agency recommends that the to-be-marketed product be evaluated in your clinical studies. If you plan to use a device which is different from the to-be-marketed version in your future BLA, you should provide a comparison of the two (b) (4) highlight any differences and provide information demonstrating that the differences do not significantly impact the product's essential performance requirements (EPRs).

Additional Comments

For the purposes of initiating clinical trials with your device constituent you should provide information satisfying #1, #2 below for EPRs only (excluding design validation), and #4 for clinical batches being used in the trials, as described below. Alternatively, provide a valid risk-based justification for not providing the information prior to clinical use. All other information is intended to inform your product development and should be provided in any future marketing application(s).

The following general feedback is related to your device constituent only. As the owner of the combination product it is expected that you maintain the quality control strategy, including design controls, for the device constituent parts of your product.

For more information regarding cGMP requirements for combination products please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

You should identify the subset of design requirements necessary for your device constituent to safely and effectively achieve the combination product's intended use. For reference, this subset of design requirements should be referred to as Essential Performance Requirements (EPRs). Other internally established terminology, such as Critical Quality Attributes (CQAs), Key Performance Indicators (KPIs), etc. may be considered equivalent to EPRs if the definition is consistent with that of EPRs and the requirements are applied to the control strategy in the same manner as EPRs. Your EPRs should consider the desired level of reliability of the product and level of risk associated with failure.

If you intend to refer to documentation (e.g. verification test reports) held within another submission and/or master file, be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.

It is recommended that you refer to the eCTD Technical Conformance Guide published in September 2016 (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf) when determining the location of the following information within your submission.

Provide the following information, at a minimum, to support the device constituent parts of the combination product:

1) Device Description Documentation
a) A complete and detailed description of your device constituent design and delivery system, including any novel features and/or functionalities. This may include engineering drawings and detailed descriptions of the individual device constituent components.
b) The principles of operation of your device, from beginning to end of the activation process, in which you explain the drug delivery mechanisms (e.g. mechanical, electrical, etc.) of your device constituent.
c) If the device constituent is being used in an investigational manner, include device labeling stating that the device is for investigational use only.

2) Design Control Documentation
a) Design Inputs/Outputs – A complete and detailed description of the device constituent design inputs and outputs per 21 CFR 820.30, specifically the design requirements/specifications documentation with objective acceptance criteria. Ensure that you clearly describe the acceptability of your design inputs and outputs within the context of the intended use of your combination product. The design inputs and outputs should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, environment of use, etc.
i) EPR Identification – (b) (4)

- (b) (4)
- (b) (4)

In addition to the EPRs listed above, we recommend you develop an EPR related to the mixing / reconstitution function of your device constituent. We also recommend that you assess these EPRs during product stability studies.

b) Design Verification Documentation – Verification testing documentation should include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design inputs of the device constituent. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product.

You should use a statistically significant sample size for verification testing. Provide valid justifications for the acceptability of any test results that do not pass its acceptance criteria.

i) As part of design verification, you should verify the EPRs with the to-be-marketed version of the device constituent and the intended biologic/drug product. However, if you plan to rely on verification testing conducted with a surrogate be sure to provide a scientific rationale for the acceptability of the surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). If available, results of stability / shelf-life testing may be provided if the to-be-marketed version of the device constituent and intended drug/biologic product are used.

c) Risk Analysis Documentation – Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.). Refer to recognized consensus standard ISO 14971 “Medical devices - Application of risk management to medical devices” or device specific Guidance for more details.

d) Design Validation Documentation –Provide design validation information demonstrating that devices conform to defined user needs and intended uses. Design validation information should be from production units (or equivalents) under actual or simulated use conditions.

e) Stability / shelf-life testing and shipping studies. You should provide documentation that ensures the to-be-marketed version of the combination product maintains the EPRs up to the labeled date of expiry and after actual and/or simulated shipping. Stability/shelf-life testing and shipping studies may be incorporated into design verification testing.

f) Lot release specifications. In your lot release specifications include the EPRs. If you intend to propose alternative control strategies for the EPRs, we recommend requesting specific feedback regarding your strategy.

3) Traceability Documentation

It is recommended that a traceability matrix is provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the EPRs are highlighted for ease of review. While a traceability matrix can take many forms, the Agency has provided a high-level example for reference:

Patient / User Needs	Design Input(s)	Design Output(s)	Verification	Validation	Shelf Life / Stability (Y/N)*	Shipping (Y/N)*	Lot Release (Y/N)*

*These columns are applicable only for EPRs

4) Considerations specific to your device constituent
   a) In addition to the EPRs listed above, we recommend you develop an EPR related to the mixing function of your device constituent. Mixing of the drug product should also be evaluated at the end of the intended shelf life of the combination product. – You should add whichever endpoint(s) you established to ensure proper mixing of the drug product to your stability studies; this is recommended to ensure the mixing functionality of the device performs as intended throughout the defined shelf life of the combination product.

2.2. Nonclinical

Question 18:
Does the Agency agree that the completed pre-clinical program supports the BLA submission of nemolizumab?

FDA Response to Question 18:
Yes, we agree that your nonclinical program appears reasonable to support the BLA submission of nemolizumab. We remind you that updated information regarding carcinogenicity risk assessment should be provided in your BLA submission (refer to the nonclinical comments contained in the meeting minutes dated 03/23/2018).

2.3 Clinical Pharmacology

Question 8:
The PK profile and the immunogenicity of nemolizumab has been evaluated in Phase 1, Phase 2a, and Phase 2b clinical studies conducted on healthy volunteers and subjects with moderate to severe AD. Does the Agency agree that the clinical pharmacology program is adequate to support the Phase 3 studies in adults and adolescents with moderate to severe AD?

FDA Response to Question 8:

We acknowledge that you completed one Phase 1 and two Phase 2 studies in healthy volunteers and subjects with moderate to severe AD. We also acknowledge that you plan to use a new formulation and a new presentation (DCS) of nemolizumab for the proposed Phase 3 trials, and your analytical comparability

studies are ongoing for the drug substance and the drug product. To support your Phase 3 trials, we recommend that you conduct a clinical trial to evaluate PK comparability of nemolizumab between the drug substance and product used in the Phase 2b study and the drug substance and product to-be-used in Phase 3 trials prior to initiating your Phase 3 trials. The PK comparability study should be conducted in an adequate number of healthy subjects. The protocol for the PK comparability trial should be submitted for our review.

Meeting Discussion:
To support PopPK approach for establishing PK similarity, the sponsor submitted new modeling and simulation data before the meeting (see sponsor attachment). The Agency stated that although the PK/PD approach could be a viable approach, it was premature to provide any agreement based on the new evidence that was submitted.

Question 9:
Does the Agency agree that the clinical pharmacology program is adequate to support the BLA submission of nemolizumab and adult and adolescents with moderate to severe AD?

FDA Response to Question 9:
It is premature to provide any agreement at this stage as PK assessment to support dosing in adolescent subjects is pending. There are significant body weight effects on drug clearance and volume of distribution based on your popPK analysis. Provide additional justification whether a body-weight based dosing or a flat dosing should be used in your adolescent clinical trial. See response to Question 1.

Meeting Discussion:
The Agency acknowledged the Sponsor's plan to conduct a PK study in adolescent subjects prior to initiating the Phase 3 trials. The Agency further recommended that although a flat-dose appears reasonable at this stage, the Sponsor should re-visit dosing based on PK experience in adolescent subjects and risk-benefit assessment.

Question 10:
The Sponsor performed a popPK analysis based on concentration data from Phase 1, Phase 2a, and Phase 2b clinical studies. Exposure data from the Phase 3 studies will be used to update the model. Does the Agency agree that the population PK model is robust and adequate to 1) describe the nemolizumab pK profile in subjects with AD and 2) to identify covariates with significant impact on the nemolizumab PK profile in subjects with AD?

FDA Response to Question 10:
Your popPK approach is reasonable. The adequacy of the analysis will be determined after we review the data and the final report.

Question 11:
The Sponsor has developed specific PK/PD models for each of the primary clinical endpoints (EASI, IGA, and pruritus numeric rating scale). Does the Agency agree that the relationships between nemolizumab plasma concentrations and primary clinical endpoint changes are adequately addressed by the developed PK/PD models?

FDA Response to Question 11:
Your PK/PD approach is reasonable. The adequacy of the analysis will be determined after we review the data and the final report.

Question 12:
The Sponsor use lyophilized powder for solution supplied in single-use vials (Vial) for administration of nemolizumab in previous clinical studies including the Phase 2b dose ranging study RD.03.SPR.114322. In the Phase 3 clinical studies, the Sponsor plans to administer nemolizumab using lyophilized powder for reconstitution in a dual chamber syringe (DCS). Analytical comparability studies are ongoing for the drug substance and drug product. It is anticipated that the results from these studies will meet the acceptance criteria. Therefore no clinical PK comparability studies will be performed. Does the Agency agree?

FDA Response to Question 12:

No. We do not agree. See response to Question 8.

2.4 Clinical

Question 1:
Based on the Phase 2b clinical and PK results, a 30-mg dose every 4 weeks with a loading dose of 60 mg is the final dose and regimen to be evaluated in the pivotal treatment phase of the Phase 3 studies. In the maintenance phase of the pivotal Phase 3 studies, the Sponsor plans to compare 2 treatment regimens: Q4 and Q8 week injection of the 30-mg dose. Dose the Agency agree?

FDA Response to Question 1:
There is no significant difference of dose response in your Phase 2b trial with dose range from 10 mg to 90 mg. We recommend that you use your PK/PD modeling to further justify the dose to be evaluated in the pivotal Phase 3 trials. We also encourage you studying 2 doses (e.g., 30 mg and a lower dose) in the pivotal Phase 3 trials.

Meeting Discussion:
The Agency recommended that the Sponsor submit additional modeling and simulation PK and efficacy data to support their dose selection. The Agency

continues to recommend evaluation of a second dose in addition to the 30mg dose proposed by the Sponsor in the Phase 3 trials.

Question 2:
Does the Agency agree that based on the Phase 2b results, a 16-week initial treatment period is acceptable to determine the primary and secondary endpoints in comparison to placebo?

FDA Response to Question 2:
This is acceptable.

Question 3:
The Phase 3 pivotal studies will consist of 2 pivotal studies with an initial treatment period of 16 weeks, followed by a maintenance treatment of 32 weeks, and an open-label, long-term, safety extension study with a 104-week treatment period.

Question 3a:
Does the Agency agree that the proposed design of the Phase 3 studies (including study population, primary and key secondary efficacy endpoints, safety assessments, sample size, and duration of treatment and follow-up) will support the BLA submission?

FDA Response to Question 3a:

Overview of Study Design
You propose to conduct two identical, randomized, placebo-controlled, double-blind, multicenter, parallel-group studies (SPR.118161 and SPR.118169) in adults and adolescents, to assess the efficacy and safety of nemolizumab in subjects with moderate-to-severe AD and associated pruritus not adequately controlled with topical treatments.

The primary objective is to assess the efficacy and safety of nemolizumab (CD14152) after a 16-week treatment period. The secondary objective is to evaluate the efficacy and safety of maintenance treatment with nemolizumab (CD14152) for up to 48 weeks.

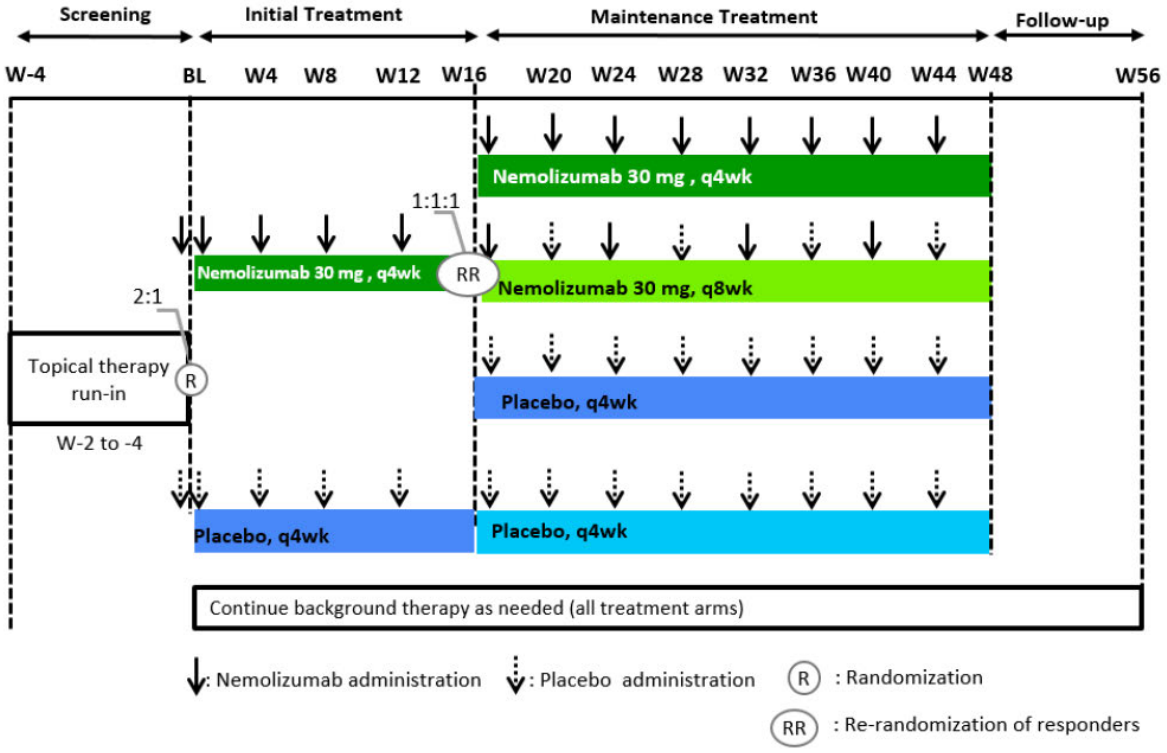
Clinical responders at Week 16 (i.e., the end of initial treatment/beginning of maintenance) will be re-randomized (1:1:1) to different treatment regimens (injections every 4 weeks [Q4W] or every 8 weeks [Q8W] of nemolizumab [CD14152] or placebo Q4W).

Clinical responders are defined as:

- Investigator's Global Assessment (IGA) of 0 [clear] or 1 [almost clear] AND improvement in PP NRS ≥4 from Baseline to Week 16, **OR**

- Eczema Area and Severity Index (EASI)-75 AND improvement in Peak (maximum) pruritus NRS (PP-NRS) ≥4 from Baseline to Week 16.

The schema for the pivotal Phase 3 studies is below:



Study Population and Sample Size

You plan to enroll approximately 750 subjects aged ≥ 12 and ≤ 70 years into each pivotal Phase 3 study (at least 130 adolescent subjects aged 12 to 17 years). Enrollment of subjects aged 12 to 17 years will begin after an independent data monitoring committee (IDMC) has assessed interim safety data from the phase 2 study, Protocol 116912, and provided recommendations to the sponsor, who will then determine the eligibility of this age group for enrollment in the study.

For study eligibility, subject must meet the following criteria:

- Chronic AD that has been documented for at least 2 years before the screening visit and confirmed according to American Academy of Dermatology Consensus Criteria
- EASI score ≥ 16 at both the screening and baseline visits
- IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits
- AD involvement ≥ 10% of BSA
- PP-NRS score of at least 4.0

These inclusion criteria are generally acceptable; however also see our other responses. Unless there is a safety concern, we do not recommend an upper bound age limit for study eligibility.

You also plan to conduct an open-label extension (OLE; SPR.118163), safety study with a 104-week treatment period. The OLE will enroll approximately 1300 subjects from the Phase 2 (114322 and 116912) and Phase 3 (118169 and 118161) studies, including an estimated 200 adolescents (aged 12 to 17 years).

The number of subjects proposed for the OLE is acceptable. However, please provide the rationale for allowance of enrollment of non-responders at Week 16 into the OLE. Also, please provide the rationale for the Q4W dosing in the OLE, when you will be evaluating Q4W and Q8W dosing as maintenance treatment in the pivotal studies.

Primary and Key Secondary Endpoints

Co-Primary Endpoints

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from baseline) at Week 16
- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16

Key Secondary Endpoints:

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 4
- Proportion of subjects with an improvement of sleep disturbance NRS (SD NRS) ≥ 4 at Week 16
- Proportion of subjects with an improvement of PP NRS ≥ 4 at Weeks 2 and 1
- Proportion of subjects with EASI-75 **and** improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with IGA success **and** improvement of PP NRS ≥ 4 at Week 16

You will evaluate primary and key secondary endpoints for the following populations:

- Baseline PP NRS ≥ 4 (full population)
- Baseline PP NRS ≥ 7

The co-primary endpoints of IGA success and EASI-75 at Week 16 are acceptable for an indication of treatment for atopic dermatitis. The endpoint of improvement of PP-NRS ≥ 4 from baseline to Week 16 is an acceptable secondary endpoint. See response to Question 3b.

You did not discuss your rationale for the proposed evaluations of endpoints according to baseline PP-NRS severity.

Safety Assessments

Safety parameters will include adverse events (AEs), AEs of special interest (AESIs), treatment-emergent AEs, physical examination, vital signs, clinical laboratory tests, electrocardiogram, and respiratory examination and related respiratory assessments (Asthma Control Test, peak expiratory flow) for subjects with a history of asthma or who develop de novo asthma. An IDMC will review and monitor subject safety on an ongoing basis. The IDMC will provide recommendations regarding the safety of subjects.

The following AEs will be considered AESIs: injection-related reactions (anaphylactic reactions, acute allergic reactions requiring treatment, severe injection site reaction i.e., lasting > 24 hours), newly-diagnosed asthma or worsening of asthma, infections (any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/ antifungals for > 2 weeks), peripheral edema (limbs, bilateral), facial edema, and elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN).

The proposed safety assessments are acceptable.

Duration of Treatment and Follow-up

The Phase 3 pivotal studies will consist of an initial treatment period of 16 weeks, followed by a maintenance treatment of 32 weeks. Follow-up visit will be conducted 12 weeks after the last study drug injection (for subjects who decline or are not eligible to enter the OLE study).

The OLE will consist of a 104-week treatment period and an 8-week Follow-up Period, 12 weeks after the last dose of study medication.

The durations of treatment in the Phase 3 pivotal studies and the OLE study may be acceptable. You indicate that 12 weeks post-treatment corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously Q4W (p. 7 of draft protocol 118161). We generally consider post-treatment follow-up through five half-lives to be reasonable.

Question 3b:

Does the Agency agree the Phase 3 program supports the desired indication (Section 1) and Clinical Studies Labeling (Section 14) as proposed in the Draft Target Product Profile?

FDA Response to Question 3b:

You propose the following indication: "treatment of moderate-to-severe atopic dermatitis (AD) (b) (4) in adult and adolescent patients, who are inadequately controlled by topical therapies."

You propose labeling outcomes for the following endpoints in "Clinical Studies" (Section 14):

- The proposed (b) (4) co-primary endpoints: IGA 0 or 1, EASI-75, (b) (4)
- PP-NRS Improvement ≥ 4 for Overall Population (b) (4)
- (b) (4)
- Maintenance of effect

We do not agree that your proposed Phase 3 program is designed to (b) (4) (b) (4) We also do not agree with your proposed (b) (4) in the Clinical Studies section of the label.

(b) (4)

Your program may support inclusion of outcomes for the "PP-NRS improvement ≥ 4" endpoint in the Clinical Studies section of the label. (b) (4)

(b) (4)

Meeting Discussion:

The Sponsor inquired about the required endpoint for establishing (b) (4)

(b) (4)

(b) (4)

(b) (4)

Post-Meeting Addendum:
For the maintenance part of the trial, you are proposing re-randomization criteria to be based on:

- Investigator's Global Assessment (IGA) of 0 [clear] or 1 [almost clear] AND improvement in PP NRS ≥4 from Baseline to Week 16, **OR**
- Eczema Area and Severity Index (EASI)-75 AND improvement in Peak (maximum) pruritus NRS (PP-NRS) ≥4 from Baseline to Week 16.

The recommended primary efficacy endpoint for atopic dermatitis is success on IGA with EASI-75 as a key secondary (or co-primary) endpoint; therefore, you may consider maintenance of response(s) for these two endpoints (i.e., without the requirement of "improvement in Peak (maximum) pruritus NRS (PP-NRS) ≥4 from Baseline to Week 16").

Question 4:

(b) (4)

FDA Response to Question 4:
We do not agree. See our previous responses.

Question 5:
Does the Agency agree with the proposed strategy to assess sleep disturbance, in order to support data collected in the Phase 3 clinical program?

FDA Response to Question 5:
No. We do not agree.

In principle, your planned qualitative and quantitative activities appear reasonable. While we are open to review the sleep disturbance-related data, we remained concerned regarding the adequacy of the SD NRS and the Subject Sleep Diary in fully supporting this concept. Please refer to the FDA Meeting Minutes dated September 17, 2018.

The concerns are outlined below:

- A single item NRS cannot fully assess the multidimensional concept 'sleep disturbance'.

- The content and item wording of the Subject Sleep Diary. For example, patients may not be able to reliably answer the following items as they may either asleep during that time or they may not understand the item wording:
  - Item 3: How long did it take you to fall asleep?

Item 4b: How many times did you wake up due to itching, not counting your final awakening?

- Item 5a: In total, how long did the awakenings last?
- Item 5b: In total how long did the itch-related awakenings last?

If you wish to proceed with these instruments in your phase 3 clinical trial, you may do so at your own risk. This will be a review issue.

Submit your psychometric study protocol for review.

Additional comments on the assessment of sleep disturbance may be provided at a later date.

Meeting Discussion:
The sponsor stated they will submit the final qualitative report to the Agency for review. The Agency recommended that the sponsor also submit the patient transcripts, if available, with the final qualitative report.

The Agency asked the sponsor to clarify how the Subject Sleep Diary will be utilized in future studies. The sponsor stated that the diary is intended to be used as exploratory endpoint to inform the SD NRS. The sponsor asked the Agency's thoughts on elevating the Subject Sleep Diary in the endpoint hierarchy. (b) (4)

The sponsor expressed interest in a separate COA-focused meeting.

Question 6:
Does the Agency agree with the proposed strategy to further validate the MCID of 4 for the SD NRS?

FDA Response to Question 6:
See FDA response to Question 5.

Question 7:
The Sponsor is proposing the use of PCS and (b) (4) as appropriate anchor scales for supportive PRO validation. Does the Agency agree?

FDA Response to Question 7:

The proposed Pruritus Categorical Scale (PCS) is problematic. The PCS measures the concept of pruritus severity. Generally, anchors should measure the same concept of interest as the target PRO (i.e., SD NRS). While the PCS may be used as a supplemental anchor, we encourage you to include an anchor measuring the severity of sleep disturbance.

If you proceed with the use of the PCS, we offer the following comments:
Remove the parenthetical text as the descriptors do not appear to be distinct. Each response option should be distinct and non-overlapping and should represent a clinically meaningful gradation of disease (e.g., the itch/scratching in Grades 1 and 2 may still be bothersome and the itch/scratching in Grade 1 may also disturb sleep).

- Use the term itch versus pruritus to ensure patients interpret and understand this concept.

Meeting Discussion:
The sponsor stated that they acknowledge the Agency's comments on their proposed anchor scales and plans to use anchor scales similar to the examples provided by the Agency (i.e., patient global impression of severity (PGIS) and patient global impression of change (PGIC). The Agency encouraged the sponsor to use multiple anchors to help inform the threshold(s) of meaningful within-patient score change in the target instrument (e.g., SD NRS). The Agency suggested that the sponsor could potentially use the Subject Sleep Diary Item #7 as an additional anchor.

Question 13:
At the time of BLA submission, combined exposure data from multiple nemolizumab studies across indications, which includes all well-controlled studies and open-label extension studies, will provide a minimum of 775 subjects exposed for 1 year. Does the Agency agree?

FDA Response to Question 13:
You indicate that the one-year exposure data at the time of BLA submission will be largely from subjects from the pivotal and OLE AD studies, with exposure at or above the 30 mg Q4W dose level. Additional studies in an AD population are ongoing, two of which are sponsored by Maruho; these studies will also contribute to the one-year safety database.

You anticipate an estimated 936 subjects with one-year exposure, including approximately 115 adolescents, at the time of BLA submission.

A safety database of 936 subjects with one-year exposure, at or above the dosing (dose and frequency) proposed for the marketplace, including approximately 115 adolescents, at the time of BLA submission is acceptable.

2.5 Biostatistics

Question 14:
Does the Agency agree with the proposed analysis of primary (co-primary and/or key secondary) endpoints?

FDA Response to Question 14:
Your proposal to analyze the co-primary and secondary efficacy endpoints (all binary) using the Cochran-Mantel-Haenszel (CMH) test stratified by the factors used to stratify the randomization appears reasonable.

You propose to analyze the continuous “additional” secondary efficacy endpoints using a mixed-effect model for repeated measures (MMRM). While these endpoints are not included in the multiplicity testing strategy and thus considered exploratory, it should be noted that an approach that incorporates information from each visit might not be clinically meaningful, yet the analysis might yield a statistically significant treatment effect by considering the overall data. Therefore, if you decide to include an appropriate continuous secondary endpoint in the multiplicity testing strategy, then the analysis for such an endpoint should be based on only the data from one timepoint (e.g., Week 16); however, modeling approaches using all timepoints may be used as supportive analyses.

Question 15:
Does the Agency concur with the proposed approach to handle the multiple testing of primary (co-primary and/or key secondary) endpoints?

FDA Response to Question 15:
The approach to handle the multiple testing of endpoints should be based on the endpoints agreed upon with the Agency; therefore, see responses to Questions 3a, 3b, 4, and 5 for comments regarding endpoints.

Question 16:
Does the Agency agree with the proposed approach to handle the missing data?

FDA Response to Question 16:
Your proposal to use non-responder imputation (NRI) for the handling of missing data for the co-primary and key secondary efficacy endpoints (all binary) appears reasonable.

You propose to use the multiple imputation (MI) approach as a sensitivity analysis for the handling of missing data. We recommend the protocols prespecify the complete details about MI, including the method to impute the missing data, the number of imputations, and seeds to ensure the results are not data driven. In addition to your proposed sensitivity analyses, we recommend including a tipping point analysis for the co-primary efficacy endpoints as a sensitivity analysis for the handling of missing data.

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 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.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be 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 that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that 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 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 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. 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 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 (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. 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 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 the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD

Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

Office of Scientific Investigations (OSI) Requests

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

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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 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 (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

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

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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
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