

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761390Orig1s000

**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 26, 2023. The purpose of the meeting was to discuss the content and format of your proposed BLA submission for the treatment of prurigo nodularis in adults.

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



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: April 26, 2023; 11:00am-12:00pm
Meeting Format: Teleconference

Application Number: IND 117122
Product Name: nemolizumab
Proposed Indication: For the treatment of prurigo nodularis in adults
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 Alesh, 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
Zarif Jabbar-Lopez, 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
Xiaoxiao Chen, Principal Biostatistician
Regis Schulz, Head of Global Regulatory Affairs
Erik Bjornson, Head of Global Biologics Regulatory Strategy
Mary Chiavelli, Head of Global Biologics Regulatory Strategy

Amy Campbell, Head of Nemolizumab Regulatory Strategy
Joyel Morris, Global Biologics Regulatory Strategy Director
Paloma Grasser, Sr. Regulatory Strategy Manager

1.0 BACKGROUND

We have had the following meetings with you:

- March 1, 2023; Breakthrough Therapy Designation
- October 26, 2022; Breakthrough Therapy Designation Multidisciplinary
- September 26, 2022; Guidance
- September 8, 2021; Guidance
- December 1, 2020; Guidance
- May 20, 2020; End of Phase 2
- January 27, 2020; Guidance

We have sent the following correspondences:

- November 3, 2022; Intent to Rescind Breakthrough Therapy Designation
- November 2, 2021; Initial Pediatric Study Plan- Agreement
- September 21, 2021; Advice
- July 2, 2020; Initial Pediatric Study Plan- Written Response
- November 25, 2019; Grant Breakthrough Therapy Designation Request
- July 12, 2019; Deny Breakthrough Therapy Designation

2.0 DISCUSSION

2.1. Clinical Pharmacology

Question 1:

Does the Agency agree on the content and format of the Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods?

FDA Response to Question 1:

The proposed content and format of the Module 2.7.1 Summary of Biopharmaceutical 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. We also note that the ELISA assay used for the PN studies is different from those used in prior studies [REDACTED] (b) (4). If you have conducted cross-validation assessment of this ELISA assay with prior assays, you should include a summary of those results under this section.
- It is unclear if you have conducted a bridging study between the dual chamber syringe [DCS] and dual chamber cartridge assembled with auto-injector

[DCC-AI] presentations of your product. Please note that if the formulation/presentation used in the pivotal study is different from the to-be-marketed presentation you will need to establish a clinical bridge between the two presentations and submit the results and the dataset in SAS transport (XPT) format in the BLA. This will be a review issue.

Meeting Discussion:

The sponsor presented the information on slide #3 of their enclosed slides. The Agency had no further comment.

Question 2:

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

FDA Response to Question 2:

The proposed content and format of the Module 2.7.2 Summary of Clinical Pharmacology Studies appears reasonable.

We acknowledge that you plan to include the executive summary of the ISI in Module 2.7.2.4 (Special Studies). 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 3:

Does the Agency agree that the PN-specific population PK and PK/PD approaches and the proposed datasets will be sufficient to enable FDA's Pharmacometric team review?

FDA Response to Question 3:

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:

The sponsor presented the information on slide #4 of their enclosed slides. The sponsor indicated that they do not plan to provide exposure-response (ER) relationships for the secondary endpoints. The Agency clarified that whether or not any additional ER analysis for secondary endpoints will be required will be a review issue.

2.3. Clinical

Question 4:

Does the Agency agree that the clinical studies planned for inclusion in the BLA submission are adequate for the evaluation of the safety and efficacy of nemolizumab and supportive of the intended indication of treatment of prurigo nodularis in adults?

FDA Response to Question 4:

The proposed content of the application appears adequate for filing.

Question 5:

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 5:

Yes.

2.4. Biostatistics

Question 6:

Does the Agency agree that the content and format of the study datasets to be submitted are sufficient to support the filing and review of the PN BLA?

FDA Response to Question 6:

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.115828, 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 7:

Does the Agency agree with the proposed efficacy analysis for the ISE as presented in the PN ISE Statistical Analysis Plan (SAP)?

FDA Response to Question 7:

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 8:

- a) Does the Agency agree with the proposed cut-off date of 10 Mar 2023 for the PN 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 PN BLA to support the Agency's assessment of nemolizumab in the proposed indication of treatment of PN in adults?

FDA Response to Question 8:

- a) Yes.
- b) Yes, your proposal appears reasonable. Additional information may be requested during the course of the BLA review.

Question 9:

- 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 PN LTE study, for the completed and ongoing additional studies conducted by the Sponsor and another Sponsor (b) (4) in PN 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 9:

- a) Yes.
- b) Yes, your proposal appears reasonable. Additional information may be requested during the course of the BLA review.

2.6. Regulatory

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

Question 10:

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 PN BLA?

FDA Response to Question 10:

From a technical perspective (and not content related), the proposed Table of Contents is acceptable.

Meeting Discussion:



Question 11:

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 11:

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 12:



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](https://www.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.

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

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 Information⁶ and Pregnancy and Lactation Labeling Final Rule⁷ 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.

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
05/01/2023 09:48:34 AM



IND 117122

MEETING MINUTES

Galderma Research and Development, LLC
Attention: Amy Campbell
Head of Regulatory Affairs Project Management
14501 North Freeway
Fort Worth, TX 76177

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 March 20, 2020. The purpose of the meeting was to discuss the development program for nemolizumab for the treatment of prurigo nodularis (PN).

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, Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Additional Information



MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: May 20, 2020; 10:00-11:00am (EDT)
Meeting Format: Teleconference

Application Number: IND 117122
Product Name: nemolizumab
Indication: For the treatment of prurigo nodularis (PN)
Sponsor Name: Galderma Research and Development, LLC
Regulatory Pathway: 351(a) of the Public Health Service Act

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

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Shari Targum, MD, MPH, FACP, FACC, Acting Deputy Director, DDD
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Brenda Carr, MD, Clinical Reviewer, DDD
Barbara Gould, CPMS, Division of Regulatory Operations for Dermatology and Dentistry
Dawn Williams, BSN, Safety Regulatory Project Manager, DDD
Mohamed Alesh, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III)
Liping Pan, PhD, Clinical Pharmacology Reviewer, DCP III
Youwei Bei, PhD, Pharmacometrics Reviewer, Division of Pharmacometrics
Yasmin Choudhry, MD, Reviewer, Division of Clinical Outcomes Assessment

SPONSOR ATTENDEES

Faiz Ahmad, MS, Head of US Biostatistics
Amy Campbell, Head of RA Project Management
Cecile Cren, PhD, Head of Analytical Science, CMC
Kenny Frazier, Head of Global Prescription Development
Michael Graeber, MD, Chief Medical Advisor & Head of Medical Expertise
Paloma Grasser, Regulatory Project Manager
Zarif Jabbar-Lopez, MD, MPH, Medical Expert
Christophe Piketty, MD, PhD, Global Senior Project Leader
Jorge Puellas, PharmD, HEOR Expert
Elisabeth Rosner, PhD, Head of Toxicology

Jami Smith, Sr. Clinical Project Manager
Nathalie Wagner, Sr. Clinical Pharmacokinetics Manager

(b) (4) Prurigo
Nodularis Expert

1.0 BACKGROUND

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on [Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency](#)* (March 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We have had the following meetings with you:

- January 27, 2020 Guidance

We have sent the following correspondences:

- November 25, 2019 Grant Breakthrough Therapy

2.0 DISCUSSION

2.1. Regulatory

Question 1:

The Sponsor intends to obtain the indication of:

- a) Treatment of prurigo nodularis, if the two primary endpoints (PP-NRS, IGA) are statistically significant.
- b) (b) (4)

Does the FDA agree to proposals a) and b)?

FDA Response to Question 1:

Your proposal appears reasonable; however, the indication(s) that you receive will be a review issue. You should first test the pruritus primary endpoint (i.e., proportion of subjects that achieve at least a 4-point improvement on the PP-NRS) prior to testing the primary PN endpoint.

The protocols specify many secondary efficacy endpoints. We note that secondary efficacy endpoints intended for labeling should be limited in number, clinically meaningful, and planned with appropriate multiplicity control. As a key secondary

efficacy endpoint, you propose to evaluate the proportion of subjects achieving ≥ 4 -point improvement on the PP-NRS from baseline to Week 4. If you envision including in labeling the results for ≥ 4 -point improvement in PP-NRS at timepoints other than Weeks 4 and 16 (e.g., a figure for the proportion of subjects achieving ≥ 4 -point improvement on the PP-NRS overtime), then the other timepoints (e.g., Weeks 8, and/or 12) should be specified as key secondary efficacy endpoints and included in the multiplicity testing strategy.

Meeting Discussion:

The Agency acknowledged that the proposed testing strategy controls the type I error rate at the 5% level; however, the proposed testing strategy does not match the requirements for the proposed indications. For the claim of PN, the Agency stated that the sponsor will need to win on both the pruritus endpoint (≥ 4 -point improvement on PP-NRS at week 16) and the IGA endpoint (IGA score of 0 or 1 and 2-grade improvement at week 16). Therefore, winning on the IGA by itself is not sufficient to get the PN indication. The Agency noted that for both indications the sponsor will need to win on the pruritus endpoint; therefore, the Agency reiterated the recommendation that the sponsor test the pruritus endpoint prior to testing any other endpoints. The Agency also reiterated that secondary endpoints intended for labeling should be limited in number, clinically meaningful, and planned with appropriate multiplicity control.

2.2. Nonclinical

Question 11:

Does the FDA agree that the completed pre-clinical program supports the BLA submission of nemolizumab?

FDA Response to Question 11:

Yes, we agree that your nonclinical program appears reasonable to support a BLA submission for nemolizumab. We remind you that you should provide updated literature references and updated weight-of-evidence analysis for the carcinogenic risk assessment for your biologic product in your BLA submission. Submit all relevant data regarding the characterization of the IL-31 RA^{-/-} mouse model with the BLA. Note full literature articles, not just a reference list, should be provided in your BLA submission.

2.3. Clinical Pharmacology

Question 2:

Does the FDA agree that the clinical pharmacology program is adequate to support the BLA submission of nemolizumab in adults with PN?

FDA Response to Question 2:

We acknowledge that the PK profile of nemolizumab has been characterized in healthy subjects and subjects with AD or PN. You plan to collect blood samples for PK and immunogenicity assessment in the planned PN Phase 3 trials. With the ongoing vaccinating study, you also plan to conduct a disease drug-drug interaction study in subjects with AD. Your overall clinical pharmacology program appears adequate to support the BLA submission of nemolizumab in adults with PN.

Question 3:

The PopPK and PK/PD models were used to optimize the dosing regimen of the Phase 3 pivotal studies with a dose adjustment for subjects with high body weight. Does the Agency agree with the proposed dosing regimen?

FDA Response to Question 3:

A dosing regimen based on weight bands with a cut point of a lower versus higher dose appears a reasonable approach. However, FDA has concern with the (b) (4) cut-off. Based on Figure 17 and Figure 19 in the meeting packages, nemolizumab exposure and predicted response rates for IGA at week 16 appear to be lower in patients weighing from 90 kg to (b) (4) when treated with the 30mg Q4W dosing regimen, in comparison to the one when treated with 0.5 mg/kg Q4W.

Meeting Discussion:

There was discussion around the body weight cut-off (b) (4) for dosing. The sponsor informed the Agency that there was no observed exposure-response in the safety parameters. The Agency advised the sponsor to reconsider the proposed body weight cut-off as the currently proposed dose of 60 mg loading and 30 mg maintenance is expected to produce lower systemic exposure and lower efficacy in the subgroup of population between 90 kg and (b) (4). The Agency also advised that the sponsor could explore an interim dose between 60 mg and 30 mg as a new maintenance dose with the aim of improving efficacy. The Agency stated that they would look into the dosing proposal at the time of review of the Phase 3 protocol.

Question 4:

Does the FDA agree that the population PK model developed for nemolizumab is robust and adequate to describe the PK profile in subjects with PN and to identify covariates with significant impact on the nemolizumab PK profile in subjects with PN?

FDA Response to Question 4:

The population PK model structure appears adequate. However, only patients with AD from three clinical trials (CIM001JP, CIM003GJ and interim SPR.114322 data) were included in the analysis. The applicant should include all available PK data in patients with PN (e.g. SPR.115828, SPR.202685, SPR.203065) in the analysis when the data becomes available. FDA recommends sponsor to test the effect of disease (PN vs AD) and antibody status (ADA) on key model parameters (e.g. CL, V). The ADA should be treated as a time-dependent variable.

Question 5:

Does the FDA agree that the relationships between nemolizumab plasma concentrations and primary clinical endpoint changes are adequately addressed by the PK/PD models?

FDA Response to Question 5:

The PK/PD model appears adequate to describe the relationships between nemolizumab plasma concentrations and primary clinical endpoint changes.

2.4. Clinical**Question 6:**

The Sponsor proposed to use Investigator Global Assessment (IGA) success and improvement in Peak Pruritus Numeric Rating Scale (PP-NRS) as primary endpoints in the pivotal Phase 3 study in prurigo nodularis. The Sponsor proposes an IGA scale (ranging from 0 (clear) to 4 (severe)), with each category defined by morphological descriptors and supported by representative photos from a reference atlas. IGA success will be defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2 -point improvement from baseline) at Week 16. Does the FDA agree that the IGA scale proposed is sufficiently robust to support the efficacy claims of nemolizumab in the intended indication, treatment of prurigo nodularis?

FDA Response to Question 6:

You propose to use the following IGA scale in Phase 3:

Score	Category	Description
0	Clear	No nodules
1	Almost	Rare palpable pruriginous nodules
2	Mild	Few palpable pruriginous nodules
3	Moderate	Many palpable pruriginous nodules
4	Severe	Abundant palpable pruriginous nodules

Your scale appears reasonable.

It is not clear that the photographs clearly depict different levels of severity. For example, the photographs for moderate and severe could be interpreted as representing similar states of severity. Similarly, the photographs intended to represent "mild" appear suggestive of disease of baseline severity i.e., at least 20 nodules. Some of the photographs are in poor focus (particularly the close-ups).

Question 7:

The Sponsor intends to conduct two independent, pivotal Phase 3 studies of identical design, with the final selected dose of 30mg injected Q4W and a 60mg loading dose (with dose adjustment for subjects with body weights $\geq$ (b) (4) kg), and a 16-week treatment duration.

Does the FDA agree with:

- a) The design of the two pivotal independent Phase 3 studies
- b) The selected dose,
- c) The treatment regimen,
- d) The study duration and follow-up periods,
- e) The inclusion and exclusion criteria,
- f) The allowed concomitant medications,

To support the BLA nemolizumab in the treatment of adults with PN?

FDA Response to Question 7:

You plan to conduct two, identical pivotal Phase 3 trials, RD.06.SPR.202685 and RD.06.SPR.203065. The primary objective of the studies is to assess the efficacy and safety of nemolizumab compared with placebo in subjects $\geq$ 18 years of age with PN after a 16-week treatment period.

You plan to randomize approximately (b) (4) subjects in a 1:1 ratio to receive either nemolizumab or placebo. (b) (4) :

- Patients weighing $<$ (b) (4) kg at baseline will receive a 60 mg SC (loading dose), then 30 mg nemolizumab (or placebo) every 4 weeks (Q4W).
- Patients weighing $\geq$ (b) (4) kg at baseline will receive either 60 mg nemolizumab or placebo Q4W (no loading dose).

The study will consist of the following periods: screening period of up to 4 weeks, a 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug administration).

Design

The general design of the proposed studies appears to be acceptable.

Selected dose and treatment regimen

See clinical pharmacology comments.

Study duration and follow-up periods

We recommend that the duration of treatment be informed by dose-ranging explorations. We recommend that you consider additional post-treatment follow-up visits at more distant time points. Follow-up through two months post-treatment

seems to be a relatively short period to get a meaningful sense of the disease course following completion of treatment e.g., durability of effect/recurrence, extent of recurrence.

Inclusion and exclusion criteria

Inclusion criteria include:

- Aged ≥ 18 years at the time of screening with a
- Clinical diagnosis of PN for at least 6 months with:
 - Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs
 - At least 20 nodules on the entire body with a bilateral distribution
 - IGA score ≥ 3 : IGA (based in the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits.
- Severe pruritus defined on the PP NRS as:
 - At the screening visit (Visit 1): PP NRS score is ≥ 7.0 for the 24-hour period the screening visit.
 - At the baseline visit (Visit 2): mean of the daily intensity of the PP NRS score is ≥ 7.0 over the previous week.

The inclusion criteria are acceptable.

Exclusion criteria include:

- Unilateral pruriginous lesions
- Chronic pruritus due to other active conditions
- Recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections)
- Pregnant or breastfeeding women have recently received live vaccines
- Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, or human immunodeficiency virus antibody) at the screening visit
- Active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months

Regarding the exclusion criteria: We acknowledge that you cannot provide an exhaustive list of examples of “chronic pruritus resulting from another active condition other than PN.” However, the examples you do provide heavily favor cutaneous diseases. Ensure that the examples are sufficiently broad to prompt investigators regarding the systemic conditions that might also make for exclusion. We note that diabetes and thyroid disease are not mentioned. Prior to study participation, treatment of the underlying systemic condition(s) should be optimized per standard of care.

Allowed concomitant medications

Subjects can use their daily moisturizer, if it does not contain any compound with known anti-itch effect (e.g., menthol, polidocanol, etc.). Subjects should not change emollients or moisturizers or apply products for itch relief during the course of the study.

You will allow sedatives and antidepressants [such as benzodiazepines, imidazopyridines, barbiturates, sedative antidepressants (eg, amitriptyline), selective serotonin reuptake inhibitors (e.g., paroxetine), or serotonin-norepinephrine reuptake inhibitors], if they have been administered for at least 3 months at a stable dose before screening baseline and dose changes are not planned during the study.

The allowed concomitant medications and their conditions of use are acceptable.

Question 8:

The 52-week long-term extension study explores safety as a primary endpoint, and efficacy as a secondary endpoint. Does the FDA consider PP-NRS and Investigator Global Assessment (IGA) measured as secondary efficacy endpoints in the long-term extension study appropriate to provide evidence of long-term efficacy of nemolizumab?

FDA Response to Question 8:

The long-term extension (LTE) study is a prospective, multicenter, open-label, study that enrolls patients who completed the Phase 2 or pivotal, Phase 3 PN studies. The LTE would not provide adequate evidence of long-term efficacy of nemolizumab, as it is an open-label study.

Question 9:

Prior to the BLA, the Sponsor plans to submit a justification for the adequacy of the safety database to support the nemolizumab in the treatment of adults with PN. This will include available safety data obtained in PN patients from the Phase 2 study and the two pivotal studies and the LTE Phase 3 study. Safety data from studies conducted in healthy volunteers and patients in the AD program will also be included. Does the Agency agree that this approach is acceptable to support the size of the safety database in PN?

FDA Response to Question 9:

You state that as of 07/19/2019, 589 subjects have been exposed to nemolizumab in studies conducted in the AD, uremic pruritus, and PN indications. You plan to enroll approximately (b) (4) subjects with PN in each of the two proposed Phase 3 pivotal studies (SPR.202685 and SPR.203065). You plan to enroll approximately (b) (4) subjects in the LTE study (SPR.202699).

The primary safety data should be from the target population (PN), exposed to nemolizumab under intended conditions of use. The extent to which safety

information from other populations and other dosing regimens would be supportive of the primary safety data would be a review issue.

We agree that you should justify that your safety database is adequate to support a marketing application. Your justification should include discussion of the prevalence of PN (on p. 71, you state that, "The size of the overall target population of patients diagnosed with PN is small, thereby limiting the numbers of subjects with PN who could be exposed to nemolizumab in an adequate and well-controlled clinical study.").

Meeting Discussion:

The sponsor's proposed safety database for submission of a marketing application for PN is not acceptable. (b) (4)

We acknowledge that PN is not a common condition, but the prevalence of the disease allows for a more robust safety database. We acknowledge that treatment for PN is an unmet medical need and that nemolizumab has been granted Breakthrough Designation for this indication. We remind you that PN does not result in life-threatening morbidity or mortality. For this reason as well, you will need to provide a more robust safety database. The sponsor inquired about engaging in further discussion with the Agency after they have additional internal discussion. The Agency recommended that they submit a meeting request.

2.5. Biostatistics

Question 10:

Does the FDA agree with the following proposed statistical methodology?

- a) Statistical analysis of primary and key secondary endpoints,
- b) Approach to handle the multiple testing of primary and key secondary endpoints,
- c) Approaches to handle the missing data.

FDA Response to Question 10:

Your proposal to analyze the primary and key secondary efficacy endpoints (i.e., all binary endpoints) using a Cochran-Mantel-Haenszel (CMH) test stratified by the factor used to stratify the randomization is acceptable.

We refer you to the response to Question 1 for comments regarding the approach to handle the multiple testing. In addition, see the response to Question 1 for comments regarding the key secondary efficacy endpoints.

Your proposal to use non-responder imputation (NRI) as the primary method for handling missing data appears reasonable. As sensitivity analyses for the handling of missing data, you proposed a multiple imputation (MI) approach and a tipping point analysis. For these analyses, you plan to set the data for subjects who use rescue medication as missing after the receipt of the rescue medication. We note that such data is not missing and recommend this data be imputed as non-responders prior to conducting MI and the tipping point analysis.

2.6. Clinical Outcome Assessment

Question 12:

The PP-NRS has been validated in previous studies, and has supported approved labeling claims in various skin diseases (e.g. atopic dermatitis). The Sponsor plans to conduct further confirmatory validation (i.e. validity, reliability, responsiveness and the development of a responder definition) of the PP-NRS in PN using Phase 2 data. Does the Agency agree that the analytical strategy proposed for the PP-NRS is appropriate and sufficient to support a labeling claim in PN?

FDA Response to Question 12:

Your proposal to evaluate the measurement properties of PP-NRS (in the target population) using phase 2 data appears reasonable.

We recommend that the threshold for within-patient meaningful change (i.e., responder definition) should be derived from anchor-based methods supplemented with anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF) curves.

Inclusion of COA data in product labeling will depend on, but is not limited to the following:

- Relevance and importance of the concept(s) of interest to the target patient population
- Strengths and limitations of the instrument within the given context of use
- Design and conduct of the trial
- Adequacy of submitted data (e.g., rigorous data collection, methods to handle missing data, etc.)
- Whether the magnitude of the statistically significant treatment effect is meaningful to patients

Question 13:

The Sponsor intends to use the SD NRS supplemented by a morning diary (i.e. the Subject Sleep Diary) to assess the sleep disturbance in PN as secondary endpoints. Exploration of the responder definition, and psychometric properties of the SD NRS will be examined in PN using Phase 2 data and further confirmatory validation of the SD NRS and SSD will be conducted in Phase 3 studies. (b) (4)

(b) (4)

FDA Response to Question 13:

(b) (4)

Please refer to the FDA Preliminary Comments (atopic dermatitis) dated April 16, 2020 regarding investigating the correlation in subject responses among the responses to SSD Q10 (quality of sleep), Q11(rested/refreshed), and the Sleep Disturbance Numeric Rating Scale (SD NRS).

We acknowledge your plan (Question 13, sponsor's position, page 82/86 of the briefing package) to evaluate content validity of SD NRS and SSD via a literature review and cognitive interviews in 20 subjects with PN. We look forward to reviewing the results of your qualitative research when available.

You plan to explore the responder definition and examine the measurement properties of the SD NRS in PN using Phase 2 data, and to conduct further confirmatory validation of the SD NRS and SSD in Phase 3 studies. Please submit your psychometric analysis plan for review.

Additionally, in your phase 3 study protocol (Study RD.06.SPR.202685 Version 1.0), the SD NRS and SSD are listed under other secondary endpoints (not as key secondary endpoints). Further, it appears that these endpoints will not be adjusted for multiplicity. Endpoints that are listed under other secondary endpoints and not adjusted for multiplicity are considered exploratory and are not considered appropriate for inclusion in the product label. Please clarify whether you plan to elevate the SD NRS and SSD endpoints in the endpoint hierarchy.

For inclusion of the PRO data in the product label, also see FDA Response to Question 12.

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 Technical Conformance Guide*, 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

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>

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 page⁴ 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. 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 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

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁵

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.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

⁵ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

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 Resources⁶ and the CDER/CBER Position on Use of SI Units for Lab Tests website.⁷

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.⁸

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.⁹

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.

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁷ <https://www.fda.gov/media/109533/download>

⁸ <http://www.fda.gov/ectd>

⁹ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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*.¹⁰

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

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

¹⁰ <https://www.fda.gov/media/85061/download>

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.

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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
05/20/2020 03:09:09 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	117122
Request Receipt Date	September 26, 2019
Product	nemolizumab
Indication	For the treatment of pruritus associated with prurigo nodularis
Drug Class/Mechanism of Action	Atopic Dermatitis/Dermatitis Agents (4020010)
Sponsor	Galdmera Research and Development, LLC
ODE/Division	ODE III/DDDP
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	November 25, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough 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):

pruritus associated with prurigo nodularis

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-threatening¹?

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 therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

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 BTDR 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.

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>

The following information is from the sponsor:

Nemolizumab is a humanized anti-human interleukin-31 (IL-31) receptor A (RA) monoclonal antibody that inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction. IL-31 has been suggested to be a key player in the development of pruritus, inducing severe pruritus and dermatitis in mouse models

IL-31 is a pro-inflammatory cytokine involved in pruritus of different conditions including PN, with additional activity related to skin barrier integrity and inflammatory pathways...IL-31 is crucial for the induction of pruritus in contact hypersensitivity.

Prurigo nodularis (PN) is a chronic skin disorder that occurs in some individuals with chronic pruritus. It is characterized by intensely pruritic nodules, distributed on body sites accessible to scratching. It occurs primarily in middle-aged and older adults,¹ and there is no approved therapy. It is a reactive process that arises from repetitive, targeted, vigorous scratching. This concentrated, aggressive scratching is driven by a sensation of focal, intense pruritus.¹ The severe pruritus may cause sleep disturbances and diminished quality of life, as well as psychiatric comorbidities.² The underlying cause of the pruritus is unknown. However, approximately 50% of patients have a history of atopic dermatitis.³ A wide variety of other conditions has been associated with PN, including diabetes, thyroid disease, lymphoproliferative malignancies, chronic renal failure, hepatitis C, HIV infection, anxiety, depression, and emotional stress.^{3,4} However, a definitive causative role for any of these conditions in the development of PN has not been established. Some authors report a 50-fold upregulation of IL-31 mRNA in PN lesions,^{4,5} which underlies a rationale for the potential benefit of nemolizumab for treatment of pruritus associated with PN.

The sponsor submitted a request for Breakthrough Therapy designation for “treatment of prurigo nodularis” (i.e., treatment of the lesions themselves) on May 22, 2019. The Division denied the request, as the relied-on study (Study SRE.115828) was not designed to adequately evaluate the treatment of PN. However, the Division did find that there appeared to be a treatment effect for percent change from baseline in peak pruritus numeric rating scale (NRS). The sponsor had also evaluated a ≥ 4 -point improvement from baseline on the peak pruritus NRS and reported that the results were statistically significant; however, the sponsor did not include the actual results. The Division advised the sponsor that to request a Breakthrough Therapy designation for the treatment of pruritus associated with PN, the Division would need to review the results for ≥ 4 -point improvement from baseline on the peak pruritus NRS, which the Division considers to be a clinically meaningful endpoint.

In the current request for Breakthrough Therapy designation, the sponsor has revised the indication to “treatment of pruritus associated with prurigo nodularis.” To support the request, the sponsor is relying on the same study that they relied on in the previous request. However, in the current submission, the sponsor included results for ≥ 4 -point improvement from baseline on the peak pruritus NRS. The sponsor states that the results are from a post-hoc analysis.

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.

Primary efficacy endpoint:

- Percent change from baseline in Peak Pruritus Numeric Rating Scale (PP-NRS) to Week 4.

Additional efficacy endpoints:

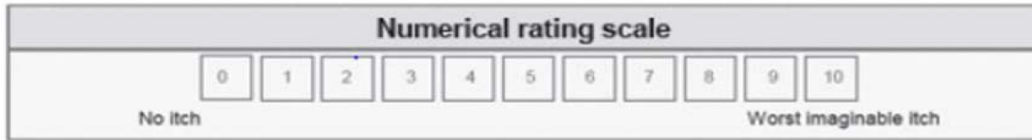
- Percent change from baseline in PP-NRS for each week

- Proportion of subjects that achieve a ≥ 4 -point reduction (improvement) in PP-NRS from baseline for each week

The sponsor did not discuss the endpoints planned for evaluation for future trials for this indication.

Peak Pruritus Numeric Rating Scale (PP-NRS):

“On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?”



- 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.*

For pruritus associated with PN, the recommended endpoint is the proportion of subjects that achieve a ≥ 4 -point reduction (improvement) on an 11-point worst/peak pruritus numeric rating scale at a specified timepoint (e.g., Week 12).

- 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:

There are no approved therapies for treatment of the pruritus of PN (or for PN itself). Counseling directed at breaking the itch-scratch cycle is a fundamental aspect of management. Corticosteroids (topical, oral, intralesional) are used in an attempt to lessen the itch and soften or flatten the lesions. Topical calcineurin inhibitors may be used.^{1,2,5} Topical capsaicin may be helpful.^{1,3} Phototherapy may be used. Other systemic therapies that are used include antihistamines, anxiolytics, opiate receptor agonists, thalidomide, methotrexate, and gabapentin.¹ Cryotherapy with liquid nitrogen may flatten lesions, and pulse-dye laser therapy may be a treatment option.¹ However, treatments are generally moderately successful, at best.^{1,5}

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

[Redacted area]

(b) (4)

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

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 design⁴, 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.*
 - *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Galderma sponsored a Phase 2a randomized, placebo-controlled, double-blind, parallel-group, multicenter study, SRE.115828, to assess the safety and efficacy of nemolizumab in subjects with PN. Study SRE.115828 was conducted at sites in Austria, France, Germany, and Poland.

The primary objective was to assess the efficacy of nemolizumab compared to placebo in the treatment of pruritus in subjects suffering from PN.

The secondary objectives were to evaluate nemolizumab compared to placebo in the treatment of lesions, quality of life and safety in subjects with PN, characterize nemolizumab pharmacokinetic (PK) profile and exposure response relationship in subjects with PN and evaluate the efficacy of nemolizumab on scratching events and sleep improvement in subjects with PN using actigraphy.

A total of 70 adult subjects with PN for at least 6 months with severe pruritus (definition: mean of the worst daily intensity of the NRS score ≥ 7 over the previous week) at baseline (measured on at least 5 days during the week preceding baseline) were randomized in the study. Subjects were randomized in a 1:1 ratio to nemolizumab or placebo treatment. Each subject received three SC injections of 0.5 mg/kg of nemolizumab or matching placebo every 4 weeks (Q4W) (at baseline, Week 4 and Week 8). The study included a screening period of up to 4 weeks, a 12-week treatment period (last study drug injection at Week 8) and a 6-week follow up period. A total of 60 (86%) subjects completed the study.

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.

Table 1: Study Design for SRE.115828

Screening (approximately 100) ↓ Randomization (approximately 70)		
	Group 1	Group 2
	N= approximately 35	N= approximately 35
Treatment	Nemolizumab 0.5 mg/kg ^a	Nemolizumab placebo
Treatment frequency	Every 4 weeks (Q4W)	Every 4 weeks (Q4W)
Treatment duration	12 weeks (last study drug injection at week 8)	12 weeks (last study drug injection at week 8)
Follow-up	6 weeks (10 weeks after the last study drug injection)	6 weeks (10 weeks after the last study drug injection)

^a If a subject weighs more than 140 kg the study drug should be prepared as for a subject who weighs 140 kg. Thus the total volume injected should not exceed 2.8 mL

Preliminary Efficacy Results:

Table 2 present the results for the protocol-specified primary efficacy endpoint (i.e., percent change from baseline in PP-NRS at Week 4), and Figure 1 presents the results for percent change from baseline in PP-NRS over time. Table 3 presents the results for the proportion of subjects that achieve a ≥ 4 -point reduction (improvement) in PP-NRS from baseline over time.

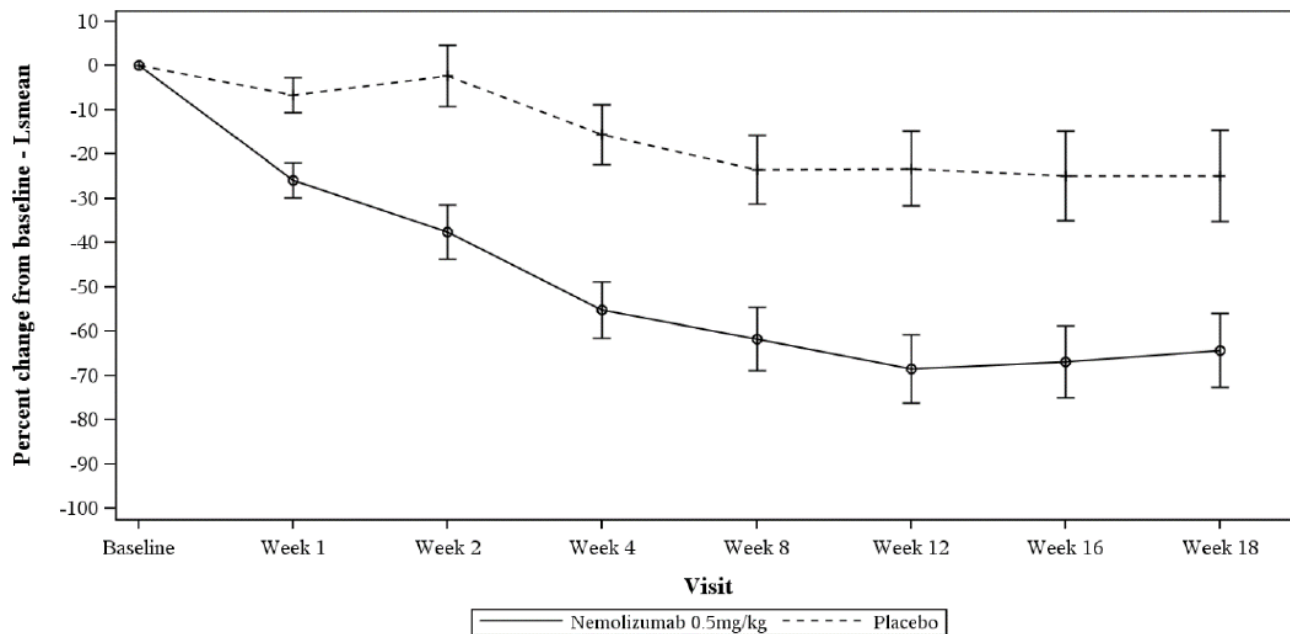
Table 2: Percent Change from Baseline in Weekly Average of the Peak Pruritus NRS at Week 4 (LOCF⁽¹⁾)

	Nemolizumab 0.5 mg/kg (N=34)	Placebo (N=36)
Baseline		
n	33	34
Mean (SD)	8.4 (1.10)	8.4 (0.86)
Median	8.3	8.3
Range	6 to 10	7 to 10
Week 4 Peak Pruritus NRS		
n	34	36
Mean (SD)	4.3 (3.16)	7.0 (1.94)
Median	4.7	7.3
Range	0 to 10	0 to 10
Percent Change from Baseline to Week 4		
n	33	34
Mean (SD)	-52.6% (33.96)	-13.8% (16.1)
Median	-45.0%	-11.8%
Range	-100% to 0%	-55% to 20%
LS Mean (SE)	-53.4% (6.19)	-15.3% (6.23)
Difference (95% CI)	-38.0% (-51.0%, -25.0%)	
P-Value	<0.001	

(1) "Missing values including those who took rescue medication were replaced by last observation carried forward (LOCF) approach."

(2) LS-mean and p-value were obtained from an analysis of variance (ANOVA) model with the change from baseline as the response and treatment, background of atopy (presence or absence) and country as fixed-effect terms.

Figure 1: Percent Change from Baseline in Weekly Average of the Peak Pruritus NRS



Error bars represent the +/- standard error from the LS-mean

Table 3: Proportion of Subjects that Achieve a ≥ 4 -point Reduction (improvement) in PP-NRS from Baseline Over Time

	Nemolizumab 0.5 mg/kg (N=34)	Placebo (N=36)
Week 1	5 (15%)	0
Week 2	34 (41%)	0
Week 4	18 (53%)	1 (3%)
Week 8	18 (53%)	2 (6%)
Week 12	18 (53%)	3 (8%)
Week 16	21 (62%)	5 (14%)
Week 18	19 (56%)	6 (17%)

Safety

The sponsor reported the incidence of treatment-emergent serious adverse events (SAEs) as being similar between groups. Neurodermatitis was said to have been the most frequently reported SAE, and all subjects were in the placebo group. The most frequently reported treatment-emergent serious adverse event (TEAE) was nasopharyngitis.

Overall summary of treatment-emergent adverse events, all causalities

Characteristic	Placebo	Nemolizumab	Total
	(N=36) n (%)	0.5 mg/kg (N=34) n (%)	(N=70) n (%)
Number of TEAEs	69	77	146
Subjects with TEAEs	24 (66.7)	23 (67.6)	47 (67.1)
Subjects with treatment-emergent SAEs	3 (8.3)	4 (11.8)	7 (10.0)
Subjects with severe TEAEs ^a	1 (2.8)	5 (14.7)	6 (8.6)
TEAE with fatal outcome	0	0	0
Subjects with TEAE leading to temporary treatment discontinuation	1 (2.8)	0	1 (1.4)
Subjects with TEAE leading to permanent treatment discontinuation	1 (2.8)	2 (5.9)	3 (4.3)
Subjects with TEAE leading to the study withdrawal	2 (5.6)	2 (5.9)	4 (5.7)

a) Missing severity was imputed to be severe prior to determining the most severe adverse event for a given subject

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:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

- 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):

The Division will encourage the sponsor to request an End-of-Phase 2 meeting to discuss the Phase 3 program. The sponsor will also need to provide their plans for assessment of the long-term safety of use of their product for the proposed indication.

- 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:

- LeCourt AP. (2019, June 28) Prurigo nodularis. *Medscape*.

2. Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. *Dermatol Clin* 36 (2018) 189–197.
3. Watsky K. Prurigo nodularis. Fowler J, ed. UpToDate. (Accessed on June 28, 2019).
4. Heymann WR. Comprehending prurigo nodularis: Ay, there’s the rub. *J Am Acad Dermatol* 2018;79:636-7.
5. Quershi AA, Abate LE, Yosipovitch G, and Friedman AJ. A systematic review of evidence-based treatments for prurigo nodularis. *J Am Acad Dermatol* 2019;80:756-64

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
11/21/2019 06:08:27 PM

SNEZANA TRAJKOVIC
11/21/2019 07:38:49 PM

KENDALL A MARCUS
11/22/2019 08:13:19 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	117122
Request Receipt Date	May 22, 2019
Product	nemolizumab
Indication	prurigo nodularis
Drug Class/Mechanism of Action	anti-IL-31 antibody
Sponsor	Galderma
ODE/Division	III/DDDP
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	July 21, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough 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): prurigo nodularis
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-threatening¹? 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:

- 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

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>

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 therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

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 BTDR 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).

Nemolizumab is a humanized anti-human interleukin-31 (IL-31) receptor A (RA) monoclonal antibody that inhibits the binding of IL-31 to IL-31RA and subsequent signal transduction. The sponsor states that “IL-31 is a pro-inflammatory cytokine involved in pruritus of different conditions including PN, with additional activity related to skin barrier integrity and inflammatory pathways”(p. 17).

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>

Prurigo nodularis (PN) is a chronic skin disorder that occurs in some individuals with chronic pruritus. It is characterized by intensely pruritic nodules, distributed on body sites accessible to scratching and occurs primarily in older adults. It is a reactive process that arises from repetitive, targeted, vigorous scratching. This concentrated, aggressive scratching is driven by a sensation of focal, intense pruritus.¹ The severe pruritus may cause sleep disturbances and diminished quality of life, as well as psychiatric comorbidities.² The underlying cause of the pruritus is unknown. However, approximately 50% of patients have a history of atopic dermatitis.³ A wide variety of other conditions has been associated with PN, including diabetes, thyroid disease, lymphoproliferative malignancies, chronic renal failure, hepatitis C, HIV infection, anxiety, depression, and emotional stress.^{3,4} However, a definitive causative role for any of these conditions in the development of PN has not been established. Some authors report a 50-fold upregulation of IL-31 mRNA in PN lesions,^{4,5} which underlies a rationale for the potential benefit of nemolizumab for treatment of PN.

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.

Primary efficacy endpoint:

- Percent change from baseline in Numeric Rating Scale (NRS) to Week 4 (weekly average of the peak).

Secondary efficacy endpoints:

- Absolute and percent change from baseline in weekly average of the peak and average pruritus NRS to each visit.
- The proportion of subjects achieving a 50%, 75% and 90% reduction from baseline in weekly average of the peak pruritus NRS.
- The proportion of subjects achieving a 4-point reduction from baseline in weekly average peak pruritus NRS.
- The proportion of subjects achieving a 4-point reduction from baseline in weekly average of the average pruritus NRS.
- Absolute and percent change from baseline in weekly average of the peak and average Verbal Rating Scale (VRS) to each visit.
- Dynamic pruritus score (DPS) at hours 24, 48, and 72 for baseline and Week 4 visits.
- Absolute change from baseline in Prurigo Activity Score (PAS) (number of lesions in a selected area) to each visit.
- PAS Item 6 (excoriation/crusts and healed lesions stages) at each visit.
- Investigator's Global Assessment (IGA) at each visit.
- Proportion of subjects achieving IGA success (defined as IGA=0[clear] or IGA=1[Almost clear] with two-point improvement from baseline) at Week 12.

The sponsor did not discuss the endpoints planned for evaluation for future trials for this indication.

- 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:

The Division does not have precedent endpoints to recommend for PN. However, our recommended endpoint for pruritus is a 4-point reduction on a peak pruritus numeric rating scale (NRS) at efficacy assessment.

- 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.

Not applicable.

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.*

There are no approved therapies for PN. Counseling directed at breaking the itch-scratch cycle is fundamental. Corticosteroids (topical, oral, intralesional) are used in an attempt to lessen the itch and soften or flatten the lesions. Topical calcineuring inhibitors may be used.^{1,2,5} Topical capsaicin may be helpful.^{1,3} Phototherapy may be used. Other systemic therapies that are used include antihistamines, anxiolytics, opiate receptor agonists, thalidomide, methotrexate, and gabapentin.¹ Cryotherapy with liquid nitrogen may flatten lesions, and pulse-dye laser therapy may be a treatment option.¹ However, treatments are generally moderately successful, at best.¹

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

(b) (4)

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 design⁴, 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.*
 - *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Galderma sponsored a Phase 2a randomized, placebo-controlled, double-blind, parallel-group, multicenter study, SRE.115828, to assess the safety and efficacy of nemolizumab in subjects with PN. Study SRE.115828 was conducted at sites in Austria, France, Germany, and Poland.

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.

The primary objective was to assess the efficacy of nemolizumab compared to placebo in the treatment of pruritus in subjects suffering from PN.

The secondary objectives were to evaluate nemolizumab compared to placebo in the treatment of lesions, quality of life and safety in subjects with PN, characterize nemolizumab pharmacokinetic (PK) profile and exposure response relationship in subjects with PN and evaluate the efficacy of nemolizumab on scratching events and sleep improvement in subjects with PN using actigraphy.

A total of 70 adult subjects suffering from PN for at least 6 months with severe pruritus (definition: mean of the worst daily intensity of the NRS score ≥ 7 over the previous week) at baseline (measured on at least 5 days during the week preceding baseline) were randomized in the study. Subjects were randomized in a 1:1 ratio to the nemolizumab group or the placebo group. Each subject received three SC injections of 0.5 mg/kg of nemolizumab or matching placebo every 4 weeks (Q4W) (at baseline, Week 4 and Week 8). The study included a screening period of up to 4 weeks, a 12-week treatment period (last study drug injection at Week 8) and a 6-week follow up period. A total of 60 (86%) subjects completed the study.

Table 1. Study Design for SRE.115828

	Screening (approximately 100) ↓ Randomization (approximately 70)	
	Group 1 N= approximately 35	Group 2 N= approximately 35
Treatment	Nemolizumab 0.5 mg/kg ^a	Nemolizumab placebo
Treatment frequency	Every 4 weeks (Q4W)	Every 4 weeks (Q4W)
Treatment duration	12 weeks (last study drug injection at week 8)	12 weeks (last study drug injection at week 8)
Follow-up	6 weeks (10 weeks after the last study drug injection)	6 weeks (10 weeks after the last study drug injection)

^a If a subject weighed more than 140 kg the study drug was prepared as for a subject who weighed 140 kg.

Preliminary Efficacy Results

Table 2. Percent change from baseline in weekly average of the peak pruritus NRS at Week 4- Primary Endpoint (ITT population)

	Placebo (N=36)	Nemolizumab 0.5 mg/kg (N=34)
Mean (SD)	-13.8 (16.10)	-52.6 (33.96)
LS-mean (SE)	-15.3 (6.23)	-53.4 (6.19)
Median	-11.8	-45.0
Min, Max	-55, 20	-100, 0
Comparison between Nemolizumab and Placebo		
Difference between treatment groups		-38.0
95% CI for the difference		(-51.0, -25.0)
p-value		<0.001

The sponsor stated that “The proportion of subjects achieving a 4-point reduction from baseline in weekly average of the peak pruritus NRS (the Division’s recommend endpoint for pruritus) was statistically significant in the nemolizumab group compared with the placebo group at all timepoints ($p \leq 0.020$).” However, the sponsor did not present the actual results.

The sponsor reported that statistically significant improvement was observed for all secondary endpoints. The results for “percent reduction of number of lesions from baseline” are presented in Table 3.

Table 3. Percent reduction of number of lesions from baseline*

	Nemolizumab (N=34)	Placebo (N=36)
Percent reduction of number of lesions from baseline	35	15

*Source: Table 4 from BTDR

Safety

The sponsor reported the incidence of treatment-emergent serious adverse events (SAEs) as being similar between groups. Neurodermatitis was said to have been the most frequently reported SAE, and all subjects were in the placebo group. The most frequently reported treatment-emergent serious adverse event (TEAE) was nasopharyngitis.

Overall summary of treatment-emergent adverse events, all causalities

Characteristic	Placebo (N=36) n (%)	Nemolizumab 0.5 mg/kg (N=34) n (%)	Total (N=70) n (%)
Number of TEAEs	69	77	146
Subjects with TEAEs	24 (66.7)	23 (67.6)	47 (67.1)
Subjects with treatment-emergent SAEs	3 (8.3)	4 (11.8)	7 (10.0)
Subjects with severe TEAEs ^a	1 (2.8)	5 (14.7)	6 (8.6)
TEAE with fatal outcome	0	0	0
Subjects with TEAE leading to temporary treatment discontinuation	1 (2.8)	0	1 (1.4)
Subjects with TEAE leading to permanent treatment discontinuation	1 (2.8)	2 (5.9)	3 (4.3)
Subjects with TEAE leading to the study withdrawal	2 (5.6)	2 (5.9)	4 (5.7)

a) Missing severity was imputed to be severe prior to determining the most severe adverse event for a given subject

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:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

The study was not designed to adequately evaluate PN, the sponsor’s proposed indication:

- The submission presents results for percent change from baseline in PN lesions; however, it appears that the number of PN lesions on the whole body for each subject was not obtained throughout the trial (baseline and subsequent visits). Instead, subjects were classified into four categories based on ranges: 1=None, 2 = 1-19 lesions, 3 = 20-100 lesions, and 4= >100 lesions. The sponsor then assigned a lesion count for each of the four categories (i.e., subjects that were “1” have 0 lesions, “2” have 10 lesions, “3” have 60 lesions, and “4” have 125 lesions). The “mean” is then based on these assigned value, which could be different than the actual number of PN lesions.
- The submission presents results for the proportion of subjects with an IGA of 0 (clear) or 1 (almost clear). However, the IGA scale included in the protocol submitted to the IND is not acceptable, as it does not include descriptors of the levels on the scale i.e., it includes only the names of the levels (i.e, “clear”, “almost clear”, “mild”, “moderate”, and “severe”). Additionally, the inclusion criteria did not specify a IGA score for study eligibility, and the sponsor did not provide the results for the baseline IGA scores. The sponsor presented the results for IGA score of 0 or 1. If the trial enrolled subjects with IGA score of 2 (mild), then these subjects would not have at least a 2-grade improvement, an element of the Division’s recommended definition of improvement on an IGA scale.
- The sponsor presented results for percent change from baseline in peak pruritus NRS, and there does appear to be a treatment effect. The sponsor did look at the results for a 4-point improvement from baseline on the peak pruritus NRS; however, the sponsor didn’t not include the actual results. The sponsor only stated that the results were statistically significant. For BTD for the treatment of pruritus associated with PN, we would want these results. However, the sponsor is not seeking this indication for BTD.

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:

As the Division does not have precedent endpoints to recommend for PN, the Division will encourage the sponsor to discuss this development program with us. Discussion will likely include a request for clarification of the indication. If the sponsor’s proposed indication is indeed treatment of PN, endpoints should need to reflect this, and protocols should include adequate assessment of resolution of the PN lesions, as well as improvement of pruritus.

14. List references, if any:

1. LeCourt AP. (2019, June 28) Prurigo nodularis. *Medscape*.
2. Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. *Dermatol Clin* 36 (2018) 189–197.
3. Watsky K. Prurigo nodularis. Fowler J, ed. UpToDate. (Accessed on June 28, 2019).
4. Heymann WR. Comprehending prurigo nodularis: Ay, there’s the rub. *J Am Acad Dermatol* 2018;79:636-7.
5. Quershi AA, Abate LE, Yosipovitch G, and Friedman AJ. A systematic review of evidence-based treatments for prurigo nodularis. *J Am Acad Dermatol* 2019;80:756-64

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/

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07/17/2019 07:37:03 AM

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