CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761224Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 103031

MEETING PRELIMINARY COMMENTS

AstraZeneca Pharmaceuticals LP
One MedImmune Way
Gaithersburg, Maryland 20878

Attention: Abir Absar, Ph.D.
Director, Regulatory Affairs

Dear Dr. Absar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tezepelumab (MEDI9929).

We also refer to your correspondence dated and received on December 14, 2020, requesting a meeting to discuss the suitability of the data package to support a marketing application for tezepelumab as an add-on maintenance treatment for severe asthma.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: March 4, 2021, from 12 PM to 1 PM EST
Meeting Location: via Teleconference

Application Number: IND 103031
Product Name: tezepelumab (MEDI9929).

Sponsor Name: AstraZeneca Pharmaceuticals LP
Regulatory Pathway: 351(a) of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 4, 2021, from 12 PM to 1 PM EST via teleconference between AstraZeneca Pharmaceuticals LP and the Division of Pulmonology, Allergy, and Critical Care. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

AstraZeneca Pharmaceuticals LP (AZ) sent in a Pre-BLA Type B meeting request dated December 14, 2020, to discuss the suitability of the data package to support a marketing application for tezepelumab as an add-on maintenance treatment for severe asthma. AZ provided the briefing materials on January 18, 2021. The expected outcome of the meeting is to address the questions provided in the briefing package

2.0 DISCUSSION

Chemistry, Manufacturing, and Controls

Question 1: Based on current schedule for the drug substance manufacturing facility at Amgen Thousand Oaks, the Sponsor would propose the

timeframe of July 12 to July 23, 2021, for the Pre-License Inspection (PLI) of tezepelumab. Does the Agency agree that this timeframe would be acceptable to conduct the PLI given the expected PDUFA goal date?

FDA Response:
The Agency cannot comment on the planning for the pre-license inspections (PLI) in support of the BLA for tezepelumab at this time. All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection. Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection. The Agency will evaluate each facility listed in the BLA to determine if a PLI is required. The manufacturing facility will be notified when an PLI is deemed necessary to support the application assessment.

Question 2: Does the Agency agree that additional drug substance and drug product stability data for the primary and commercial (validation) lots may be submitted within the first 30 days of the original BLA filing without extension of the review clock per PDUFA guidelines?

FDA Response:
The Agency expects applications to be complete at the time of submission. However, we agree that a stability update can be submitted no later than 30 days after the submission of the original application (i.e., not 30 days after BLA filing) without review clock extension.

In addition, during the review of the BLA, the Agency may request a "simple stability update" which is defined as stability data and analyses performed under the same conditions and for the same drug substance and drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA. Simple stability updates submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf life determinations.

Clinical

Question 3: Does the Agency agree that the body of evidence shown is sufficient to support acceptance and review of a BLA to assess the benefit-risk

profile of tezepelumab for the treatment of adult and adolescent patients with severe asthma?

FDA Response:
From a clinical perspective, we agree that the proposed BLA submission appears sufficient for substantive review.

Question 4: [redacted] ***Does the Agency agree*** [redacted]

FDA Response:
We agree, in principle, [redacted] whether the submitted data for tezepelumab supports use in a severe asthma population [redacted] will be a review issue.

Question 5: [redacted] ***Does the Agency agree?***

[redacted]

FDA Response:
Pending that review of the submitted data supports use of tezepelumab in a [redacted] severe asthma population, the indication statement should accurately identify the population in whom your drug was studied [redacted] will ultimately be a review issue. In addition, whether your clinical development program which included 82 adolescents (n=41 tezepelumab, n=41 placebo) will support an indication in this age group will be a review issue.

Question 6: [redacted] (b) (4) ***appears to support an indication statement*** [redacted] (b) (4) ***Does the Agency agree?***

FDA Response:
The final description of the population in the indication statement will be a review issue, taking into account the specific severity characteristics of the enrolled patients. While asthma severity categorization has evolved over time, the trial populations of NAVIGATOR and PATHWAY are reasonably described as subjects with "severe asthma", and you note that you specifically utilized GINA guidelines for severe asthma in the enrollment criteria for NAVIGATOR. In addition, see our response to Question 5, above.

Question 7: Does the Agency agree that the efficacy and safety results from NAVIGATOR and PATHWAY, together with the proposed population PK and exposure-response analysis, is expected to support the dosing rationale of tezepelumab in adults and adolescents with severe asthma?

FDA Response:
Yes, we agree.

Question 8: Data from the Phase 3 study NAVIGATOR provide confirmatory results to the Phase 2b study PATHWAY for the proposed indication and as such, the Sponsor plans to present the data side-by-side in the prescribing information. The Sponsor plans to submit data from the final database lock for PATHWAY, as presented in the CSR version 2. The Sponsor does not intend to submit interim data that were performed to accelerate the Phase 3 programme design; these data remain on file. Does the Agency agree with these plans for presentation and submission of PATHWAY data?

FDA Response:
While the content of prescribing information will be a review issue, your proposal to present efficacy and safety data from both PATHWAY and NAVIGATOR in proposed labeling is reasonable. While substantive review of data from PATHWAY will likely be based primarily on the CSR created after final database lock, since data from PATHWAY is part of the substantial evidence for approval and labeling, you should submit all documents necessary to prove that the integrity of the data was not compromised due to unblinding of sponsor personnel; we may request that you submit the interim data, if warranted.

In addition, we note that SOURCE did not demonstrate a benefit with respect to OCS

reduction for patients treated with tezepelumab. The extent and inclusion of safety/efficacy data from SOURCE in the prescribing information will be a review issue.

Question 9: The Sponsor plans to submit bioresearch monitoring (BIMO) information for the Phase 3 study NAVIGATOR and the Phase 2b study PATHWAY (confirmatory asthma exacerbation studies), and for the Phase 3 OCS-reduction study SOURCE. Does the Agency agree with the suggested approach?

FDA Response:
We agree.

Regulatory

Question 10: Does the FDA agree with the proposed inclusion of information in the Table of Contents of the electronic Common Technical Document (eCTD) to support the tezepelumab BLA?

FDA Response:
We agree.

Additional Nonclinical Comment
A safety assessment of extractables and leachables should be provided in the BLA for all primary container closure components of the device that are in contact with the drug product during storage as well as secondary container closure components where there is a potential for migration of leachables into the drug product. See USP Chapters for 1663 and 1664 for the design of extractables and leachables studies, respectively.

CMC Microbiology comments:
We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your <351(a)> BLA submission.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the <351(a)> BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

a. Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

b. Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).

c. Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

d. Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

e. Information and summary results from the shipping validation studies (3.2.S.2.5).

f. Drug substance bioburden and endotoxin release specifications (3.2.S.4).

g. Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the <351(a)> BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

a. Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.

b. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

c. Parameters for filling and plunger placement for the pre-filled syringes.

d. Parameters for filling and capping for the vials.

e. A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

f. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

g. Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

a. Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.

b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.

c. In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

d. Isolator decontamination summary data and information, if applicable.

e. Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

f. Information and summary results from shipping validation studies. For prefilled syringes/autoinjectors, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.

g. Validation of capping parameters, using a container closure integrity test.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

a. Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

b. Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

c. Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).

d. Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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

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

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

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

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

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[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] 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

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

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.

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 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. 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.

[6] https://www.fda.gov/media/84223/download

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[8]

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.

[8] 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/

COLETTE C JACKSON
02/28/2021 11:26:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103031

MEETING MINUTES

MedImmune, LLC (a wholly owned subsidiary of AstraZeneca)
One MedImmune Way
Gaithersburg, Maryland 20878

Attention: Erika Panico, RAC
Director, Global Regulatory Affairs

Dear Ms. Panico:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tezepelumab (MEDI9929).

We also refer to the meeting between representatives of your firm and the FDA on July 10, 2017. The purpose of the meeting was to discuss the results and interpretation of the phase 2b asthma study 1146, present the rationale to progress the clinical development program to Phase 3, and discuss the planned registration studies for asthma to support a marketing application for the proposed indication for tezepelumab for the treatment of severe asthma.

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

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: July 10, 2017, from 3 PM to 4:30 PM EST
Meeting Location: WO22, Conference Room 1419

Application Number: IND 103031
Product Name: Tezepelumab
Indication: Asthma
Sponsor/Applicant Name: MedImmune, LLC (a wholly subsidiary of AstraZeneca)

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director, DPARP
Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP
Erika Torjusen, M.D., Clinical Reviewer, DPARP
Sury Sista, Ph.D., Clinical Pharmacology Reviewer
Anshu Marathe, Ph.D., Clinical Pharmacology Team Leader
Robert Abugov, Ph.D., Statistical Reviewer
Yongman Kim, Ph.D., Acting Statistical Team Leader
Carol Galvis, Ph.D., Pharmacology/Toxicology Team Leader
Anup Srivastava, Ph.D., Pharmacology/Toxicology Reviewer
Colette Jackson, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

MedImmune/AstraZeneca
Asa Hellqvist, Principal Statistician, Global Medicines Development
Azin Shahzamani, Vice President, Global Regulatory Affairs
Chris Miller, Biometrics & Information Sciences Therapy Head
Colin Reisner, Head, Respiratory Global Medicines Development
Erika Panico, Director, Global Regulatory Affairs
Esther Garcia Gil, Global Clinical Lead, Global Medicines Development
Lorin Roskos, Vice President, Research and Development
Martin Jones, Director, Global Products
Mary Jane Hinrichs, Principal Toxicologist, Toxicology

Mitch Goldman, Vice President, Biologics, Respiratory Global Medicines Development
Rene van der Merwe, Senior Director, Clinical Development

Amgen
Laura Bloss, Executive Director, Regulatory Affairs

1.0 BACKGROUND

MedImmune, LLC (MedImmune) sent in a Type B meeting request dated April 10, 2017, to discuss the results and interpretation of the phase 2b asthma study 1146, present the rationale to progress the clinical development program to Phase 3, and discuss the planned registration studies for asthma to support a marketing application for the proposed indication for tezepelumab for the treatment of severe asthma. The Division granted the meeting on May 5, 2017. MedImmune provided their briefing materials on April 28, 2017. Upon review of the briefing package, the FDA sent Preliminary Comments to MedImmune on July 3, 2017. The content of that communication is printed below. On July 6, 2017, MedImmune outlined their discussion points via email in a clarification document to facilitate the discussion. This was officially submitted on July 21, 2017, and is attached to these meeting minutes under Section 6. Any discussion that took place at the meeting is captured directly under the relevant original response in Section 2.0, including any changes in our original position. MedImmune's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2. DISCUSSION

Question 1: Nonclinical Safety Program

Does the Agency agree that the nonclinical studies described are sufficient to support the Phase 3 conduct and approval of a marketing application for tezepelumab in the proposed indication?

FDA Response:
The nonclinical program described in the package is adequate to support phase 3 clinical studies and marketing.

Discussion:
No discussion was held for this response.

Question 2: Carcinogenicity

Does the Agency agree that the plans for carcinogenicity risk assessment described are sufficient to support the approval of a marketing application for tezepelumab in the proposed indication?

FDA Response:
We agree that your carcinogenicity risk assessment is sufficient to support a marketing application.

Discussion:
No discussion was held for this response.

Question 3: Overview of Planned Phase 3 Program

Does the Agency agree that the safety and efficacy data generated thus far, in addition to the data to be generated from the proposed Phase 3 clinical development program, will be sufficient for market approval of tezepelumab in the proposed indication?

FDA Response:
Pending review of the study results, the design of your clinical development program appears acceptable to support the approval of tezepelumab for the proposed indication.

Discussion:
No discussion was held for this response.

Question 4: Selection of Subject Population for the Exacerbation Studies

Does the Agency agree that:

a. The inclusion/exclusion criteria proposed by the Sponsor for the exacerbation study (Study 1) are appropriate to support the proposed indication?

FDA Response:
In general, the proposed patient selection criteria are appropriate to support the proposed indication. However, given the safety profile of your drug thus far, we question the need to exclude patients with known/suspected history of immunosuppression, immune dysfunction, or immune dysregulation. These constitute broad exclusions which could require restrictions in labeling. As such, we recommend inclusion of these patients with close safety monitoring for related adverse events, such as opportunistic infections and Guillain-Barre syndrome.

Discussion:
FDA noted that there was no apparent safety signal identified in the clinical development program to date that would preclude the inclusion of patients with evidence of immunosuppression, immune dysfunction and immune dysregulation. MedImmune agreed with this assessment and stated that these patients would not be excluded from the study population.

b. Based on data generated in adults and adolescents thus far, adolescents may be enrolled in Study 1?

FDA Response:
We agree.

Discussion:
No discussion was held for this response.

c. The number of adolescents to be enrolled in Study 1 will be sufficient to support approval of tezepelumab in patients with severe asthma aged 12 to 17 years?

FDA Response:
We note your plan to enroll 80 adolescents in Study 1 (40 subjects randomized to placebo and 40 subjects randomized to tezepelumab). While there is no requirement to demonstrate a statistically significant treatment effect in the adolescent subgroup, a robust efficacy evaluation can provide a reassuring risk-benefit assessment, in the event that a new safety signal is identified in the overall population. Therefore, we recommend that you increase the number of adolescent patients exposed to tezepelumab. Given the efficacy demonstrated with ACQ-6 and AQLQ in the phase 2b asthma study (CD-RI-MED19929-1146), it may be possible to detect a meaningful difference in these endpoints in the adolescent population with a small increase in sample size. Using the 12 week AQC-6 data from Figure 10.3.1.2-7 of the meeting package, we calculate a difference between treatment means of ~0.36 and a standard deviation of ~ 0.62. Therefore, the sample size needed to obtain 80% power would be ~50 subjects per treatment arm. (The sample size to obtain 90% power would be ~ 65 per treatment arm.) Ultimately, approval in this age group will be based on a risk-benefit assessment when examining the totality of the data.

Discussion:
No discussion was held for this response.

Question 5: Dose Selection

Does the Agency agree with the Sponsor's conclusions regarding the dose-response relationship for tezepelumab and the rationale for the selection of the 210 mg Q4W dose for the Phase 3 studies?

FDA Response:
Based on the clinical data provided, selection of the 210 mg dose administered q4w appears reasonable.

Discussion:
No discussion was held for this response.

Question 6: Clinical Safety

a. Standard safety assessments (monitoring for AEs, periodic ECGs, etc.) are planned during the Phase 3 program. Additional proposed safety evaluations in Studies 1 and 2 include adjudication of malignancies, MACE and fatal events, assessment of adverse events of special interest, prospective assessment of anaphylaxis, and evaluation of the immunogenicity of tezepelumab. Does the Agency agree that these assessments are adequate to fully characterize the safety profile of tezepelumab in support of marketing authorization for the proposed indication?

FDA Response:
In general, the proposed safety assessments are acceptable. However, based on the synopsis provided, it is unclear which adverse events will be captured as adverse events of special interest (AESI). Your final protocol should specifically outline and define the AESI. Based on the mechanism of action of tezepelumab, you should include a pre-specified methodology to monitor for opportunistic infections. A suggested list of infections that could be used to generate predefined preferred terms can be found in 'Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.' It is available for download at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Whether these safety assessments will fully characterize the safety profile of tezepelumab in support of market authorization for the proposed indication will depend on whether new safety signals are identified and ultimately, will be a review issue.

Discussion:
No discussion was held for this response.

b. Does the Agency agree that the extent of the proposed safety database will be sufficient to support approval of a marketing application for tezepelumab to be administered in the clinic?

FDA Response:
The proposed safety database appears acceptable to support approval, provided no new safety signals are identified.

Discussion:
No discussion was held for this response.

Post Meeting-Comment: For new molecular biologic products with potential immunosuppressive properties, we expect the overall safety database would include controlled safety data from ~1000 patients exposed to your product at the proposed dose or higher for at least one year. Based on our review of your program, our understanding is that your product would achieve or exceed this expectation.

c. Assuming that the PK exposure for the aPFS and LVAI are comparable to the PK exposure for vial and syringe (b) (4) (b) (4) (b) (4) ***does the Agency agree that the extent of the proposed safety database will be sufficient to support approval of a marketing application for tezepelumab*** (b) (4)

FDA Response:
We are concerned that the to-be-marketed presentation (initially the aPFS) will not be used in the controlled clinical studies. You should plan to conduct your phase 3 studies using the to-be-

marketed presentation; (b) (4)
(b) (4)

Pending review of the phase 3 study results and overall safety profile of tezepelumab (b) (4)
(b) (4)

Discussion:
FDA strongly advised that the to-be-marketed device be used in the phase 3 studies. MedImmune stated that their current plan is to use the vial and syringe in phase 3 and then conduct PK bridging studies for the accessorized pre-filled syringe (aPFS). FDA expressed significant concerns with this plan, as it introduces new risks to the BLA approval process related to the CDRH review of the new deice, site inspections, and human factor studies. FDA suggested that MedImmune proceed with the vial and syringe for the phase 3 program and use this formulation for the initial BLA submission. Then, at a later date, engage the Agency regarding the development of the aPFS (b) (4)

In line with this recommendation, FDA further stated that it is important to conduct the phase 3 program expediently, as other biologics which are ahead in their development will likely become available in the near future and could raise ethical concerns with the conduct of "placebo-controlled" trials for new biologics in asthma. These pending approvals may introduce further complexity into asthma clinical trials and require consultation of IRBs and the academic community regarding their position on placebo-controlled trials.

FDA commented that the tezepelumab phase 2b study is an important study and may be suitable for inclusion in the product label pending review of the comparability data for the two process formulations used in the phase 2 and 3 studies.

MedImmune/AstraZeneca stated they will discuss internally and contact the FDA for further feedback regarding the Product Quality and Clinical concerns.

Post Meeting Comment: In an email to Colette Jackson, dated November 2, 2017, the sponsor asked for clarification regarding the FDA response to Question 6c. The Sponsor provided the following information and question in the email:

In response to Question 6c:
"*Assuming that the PK exposure for the aPFS and LVAI are comparable to the PK exposure for vial and syringe* (b) (4)
(b) (4) *does the Agency agree that the extent of the proposed safety database will be sufficient to support approval of a marketing application for tezepelumab* (b) (4)

FDA responded:
"*We are concerned that the to-be-marketed presentation (initially the aPFS) will not be used in the controlled clinical studies. You should plan to conduct your phase 3 studies using the to-be-marketed presentation* (b) (4)
(b) (4)

Pending review of the phase 3 study results and overall safety profile of tezepelumab, (b) (4) (b) (4)

Our original intent was (b) (4) (b) (4) The underlined phrase from the preliminary advice, above, suggests that our intent was not clear in the meeting package.

We understand from the preliminary comments and from the discussion at the End-of-Phase 2 meeting that the Division's preference is for the Sponsor to use the aPFS in the controlled clinical studies, and we hope that the Division can answer the following questions:

(b) (4)

Division response: To clarify, it was the Division's understanding (b) (4) (b) (4) (b) (4) (b) (4) *Therefore, the Division recommended during the meeting that the sponsor proceed with development using the vial and syringe presentation, as not to delay development, and also to introduce the least complexity into the development program.* (b) (4) (b) (4) (b) (4) *(See discussion from meeting above.)*

Question 7: Primary Endpoint for Exacerbation Study

Does the Agency agree with the definition of the primary endpoint and proposed primary analysis for Study 1?

FDA Response:

We agree with the proposed initial analysis for the primary endpoint of study 1. However, sensitivity analyses are integral to the primary analysis, and the sensitivity analyses you describe will evaluate only a limited number of scenarios for missing data. Instead, for any endpoints proposed for inclusion on the product label, or which are in the analysis hierarchy prior to endpoints proposed for inclusion on the product label, prospectively plan sensitivity analyses that systematically and comprehensively explore the potential effect of missing data on the reliability of results, e.g., tipping point analyses. Such tipping point analyses should be two dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on treatment have worse outcomes than dropouts on placebo. The goal will be to evaluate the plausibility of the assumed expected values for missing outcomes on each treatment arm under which the conclusions change, i.e.,

under which there is no longer evidence of a treatment effect. In the tipping point analysis, ensure that all observed data is included as non-missing, regardless of adherence to treatment or use of prohibited medications. Provided analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

For secondary endpoints also, ensure that you continue to collect data regardless of adherence to randomized treatment, and that you evaluate the treatment policy estimand.

Because the treatment policy estimand is of primary importance for evaluation of efficacy, it will be critical to prevent missing data preemptively. Therefore, include in your protocol and investigator training documents standard and consistent procedures to encourage patients who discontinue treatment to return for all regularly scheduled visits for safety and efficacy assessments. In particular, ensure that: (1) the protocol and informed consent form clearly differentiate reasons for treatment discontinuation from reasons for study withdrawal; (2) the only reasons in the study report for study withdrawal are patient withdrawal of consent to contribute additional outcome information and loss to follow-up; (3) site investigators are trained to understand the importance of patient retention and prevention of missing data; (4) consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early; and (5) the protocol establishes plans to systematically and consistently attempt to contact patients who fail to actively maintain contact with the investigator, e.g., number of telephone calls, day of week and time of such calls, which calls will be made to work, home, cell phone, family, or friends, offers for transportation to clinic for evaluations if patient is unable to drive, etc.

Discussion:
No discussion was held for this response.

Question 8: Biomarkers to be Examined in the Exacerbation Study

The Sponsor has designed Study 1 to demonstrate a statistically significant and clinically relevant reduction in exacerbations over a 52-week period in a severe asthma population. In addition, (b) (4) ***biomarkers of established clinical interest: baseline specific IgE (FEIA) status and blood eosinophils. Given the limitations of other biologic therapies for asthma, it will be important to indicate that tezepelumab is effective in different biomarker populations.***

a. Does the Agency agree that the proposed analyses are sufficient to demonstrate (b) (4)

FDA Response:
We do not agree with the analysis methods you propose (b) (4) (b) (4) (b) (4) *However, we*

agree that enrollment of patients and collection of data across a broad range of biomarker values will help determine whether such biomarkers influence treatment effect.

Discussion:
MedImmune stated that they plan to present the results of subgroup analyses with associated graphical visualizations to help interpret the impact of biomarkers on treatment effect. FDA noted that it will be difficult to statistically fit non-linearities in treatment effect as a function of biomarker value. Tests of treatment by biomarker interactions and associated forest plots where treatment by biomarker interactions are significant may help provide some insight into impacts of biomarkers on treatment effect.

FDA also noted that evaluation of patient eosinophil status can be tricky, as a given patient's counts can change 20% to 30 % within a single day. Within day, and between week, variation can easily obscure results of biometric analyses. Another contributor to variability is use of multiple measurement platforms (platform = model of instrument measuring eosinophil count); for this reason, FDA recommended that the sponsor use a single measurement platform to assess eosinophil counts across all patients throughout the study.

b. Does the Agency agree that the results, if consistent across these biomarkers, would be clinically relevant for physicians?

FDA Response:
Knowledge of the intended target population and the population that is expected to obtain benefit from the medication is relevant to physicians.

Discussion:
No discussion was held for this response.

c. Does the Agency agree that the results, if consistent across these biomarkers, would enable the description of the results in these subpopulations in the Clinical Trials section of the Prescribing Information?

FDA Response:
In general, we have included the characteristics of asthma patient populations in recently approved biologics for asthma. Biomarker data (such as baseline eosinophil count) may be included as a part of this information (see package inserts for Nucala and Cinqair). Further discussion of the description of results and specific labeling is premature at this time. Based on the mechanism of action and proposed clinical study, we do not have any expectation that there would be a limitation of use of tezepelumab based on biomarker values.

Discussion:
No discussion was held for this response.

Question 9: Testing Strategy for Secondary Endpoints in Exacerbation Study

Secondary endpoints will assess the effects of tezepelumab on lung function, asthma control (ACQ-6), asthma-related quality of life, and asthma symptoms. Does the Agency agree with the proposed multiple testing strategy as outlined?

FDA Response:
We agree with your proposed multiple testing strategy for Study 1. However, for Study 2, ensure that you provide a multiple testing strategy for all endpoints which may be proposed for inclusion on the product label.

We note that you plan to administer multiple questionnaires. As the order in which these questionnaires are administered can have an effect on subsequent responses, we suggest that you administer the questionnaires in order of importance. In addition, we recommend inclusion of ACQ 5 and ACQ 7, rather than ACQ 6 and AQLQ in place of, or in addition to, ASD (further details are provided in the response to question 10a).

Discussion:
MedImmune stated that both the ACQ 7 and ACQ 5 results could be provided for the visits when FEV1 is collected. FDA clarified that the ACQ 7 is an important endpoint as it captures the FEV1 response associated with tezepelumab, which is less common for biologics, and could be clinically meaningful to physicians. FDA stated that there is precedent for inclusion of ACQ, presented as a responder analysis, in Section 14 of the label regardless of results or statistical significance. ACQ 5 results could be useful in the interpretation of the ACQ 7 results, however (b) (4)

MedImmune stated that they consider (b) (4) to be a highly relevant tool in the assessment of patients with severe asthma and would like to include those results in the product label. FDA acknowledged that there is precedent for inclusion of (b) (4) results in asthma product labels. However, the data provided indicate promising AQLQ results with dose separation and therefore in the absence of (b) (4) data, FDA recommended the inclusion of AQLQ in the phase 3 program. MedImmune stated that they will reconsider use of AQLQ.

Also, FDA stated that, to control Type 1 error, with the exception of components of statistically significant composite endpoints included in the analysis hierarchy, any endpoints to be considered for inclusion on the product label should be included in the analysis testing hierarchy.

Question 10: Assessment of Asthma Symptoms

Does the Agency agree that

a. The Asthma Symptom Diary (ASD) is a fit-for-purpose tool for assessing asthma symptoms?

FDA Response:
Use of the ASD in the phase 3 trials is at your discretion and should be supported with a rationale for its inclusion. In addition, we recommend evaluation of patients using ACQ- 5 and

ACQ-7 to assess asthma control and the associated asthma symptoms, and AQLQ to describe the degree to which these symptoms affect quality of life. We consider these endpoints to be clinically meaningful; (b) (4) (b) (4) *We refer you to the package inserts of Nucala and Cinqair for examples of how these measures are analyzed and reported in labeling. Results are best analyzed and reported as a responder analysis (in which a responder is defined as achieving an improvement in score of 0.5 or more as threshold). Your NDA submission should include a responder analysis of the ACQ and AQLQ data.*

Discussion:
The FDA stated that the responder analysis is preferred as this is what will be presented in the product labeling and is supportive of exacerbations. The FDA expressed concerns of missing data and suggested enrolling a large number of patients for a shorter period of time but greater than 3 months in duration.

b. (b) (4)

FDA Response:
(b) (4) *See response to Question 10a.*

Discussion:
No discussion was held for this response.

Question 11: Oral Corticosteroid Sparing Study

Does the Agency agree that:

a. The proposed subject population in Study 2 is appropriate to demonstrate a clinically meaningful effect with regard to the reduction of oral corticosteroid (OCS) use?

FDA Response:
We agree.

Discussion:
No discussion was held for this response.

b. The design and the primary endpoint of Study 2, percent reduction from baseline in the daily OCS dose at Week 52 post randomization as compared to placebo, will provide clinically relevant information for patients and physicians?

FDA Response:
In general, and based on the synopsis provided, we agree with the proposed design of Study 2. However, we do not agree that patients with a documented failure of OCS dose reduction within (b) (4) *prior to Visit 1 should not be required to undergo the 8 week optimization phase.* (b) (4)

(b) (4) *is a considerable duration, given the variable nature of asthma symptoms and control. Propose a shorter duration of time prior to Visit 1 in which a failed OCS reduction would exclude patients from the optimization phase; alternatively, we recommend that you should attempt OCS reduction in all participants, regardless of previous reduction failures.*

Discussion:
No discussion was held for this response.

c. (b) (4)

FDA Response:
No, we do not agree. (b) (4)
(b) (4)

Discussion:
No discussion was held for this response.

d. (b) (4)

FDA Response:
(b) (4)
(b) (4) *See response to Question 10c.*

Discussion:
MedImmune noted there are concerns with steroid sparing and it is challenging to find participants to placebo.

2.0 OTHER IMPORTANT MEETING INFORMATION

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

Office of Scientific Investigations (OSI) Requests

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

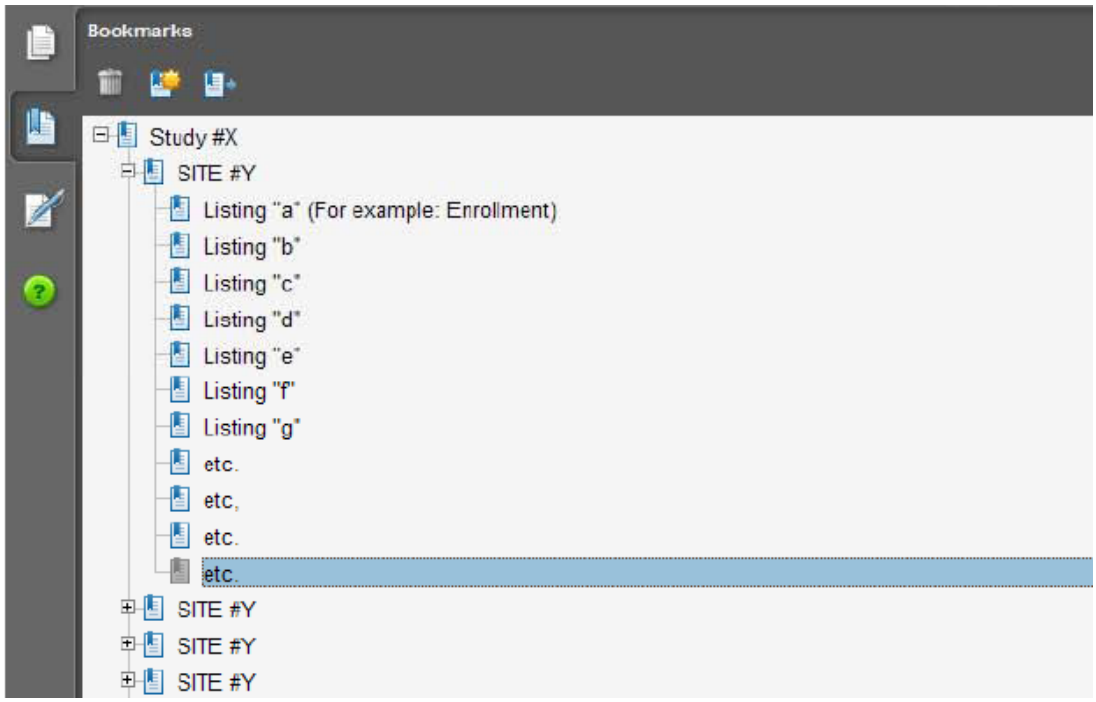
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
    b. Subject listing for treatment assignment (randomization)
    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    f. By subject listing, of AEs, SAEs, deaths and dates
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
    h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
    i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
    j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

There were no action items identified at the meeting

6.0 ATTACHMENTS AND HANDOUTS

MedImmune's clarification document sent via email on July 6, 2017, and officially submitted to the IND on July 21, 2017.

MedImmune thanks the Agency for the feedback provided supporting the tezepelumab End-of-Phase 2 meeting to be held on 10 July 2017. Below are our responses to the preliminary comments provided by the Agency on 03 July 2017, with topics for discussion noted:

Question 1: Nonclinical Safety Program

We thank you for these comments and do not feel further discussion is necessary.

Question 2: Carcinogenicity

We thank you for these comments and do not feel further discussion is necessary.

Question 3: Overview of Planned Phase 3 Program

We thank you for your agreement that a single exacerbation study and an OCS-sparing study appear sufficient to support approval of tezepelumab for an indication in severe asthma.

Question 4: Selection of Subject Population for the Exacerbation Studies

We acknowledge your agreement that studying the subject population of GINA Steps 4-5 is sufficient to support approval of this product in severe asthma.

We thank you for your comments on the inclusion of patients with immunosuppression, immune dysfunction and immune dysregulation and would like further clarification on this recommendation at the meeting.

Question 5: Dose Selection

Thank you for your feedback on dose selection for the tezepelumab Phase 3 program. We do not feel further discussion is necessary.

Question 6: Clinical Safety

We appreciate your comments, and will take them under advisement. We look forward to further discussions regarding the Sponsor's approach (b) (4) (b) (4)

Question 7: Primary Endpoint for Exacerbation Study

We do not feel further discussion is necessary and we thank you for your feedback.

Question 8: Biomarkers to be Examined in the Exacerbation Study

The Sponsor appreciates the Agency's comments on the concept of consistency of effect, and we would like to further discuss this topic at the 10 July meeting.

We agree that absence of a statistically significant effect cannot confirm a null hypothesis. To clarify, the proposed analysis incorporating interaction terms within a model is to estimate the treatment effect (and the uncertainty around it) as pre-defined subgroup analysis for categorized biomarkers. In addition, given the biomarkers are continuous, the trend plots are proposed to better understand the treatment effect (and uncertainty) across each biomarker. Based on the above, we would appreciate clarification as to whether this analysis would support determination of consistency of effect.

Question 9: Testing Strategy for Secondary Endpoints in Exacerbation Study

Thank you for your comments regarding the multiple testing strategy. We would like to discuss this point further at the End-of-Phase 2 meeting.

Inclusion of Secondary Endpoints in Testing Hierarchy (Study 2)

We note that the Agency recommends that all endpoints of Study 2 (b) (4) (b) (4) be included in the multiple testing hierarchy. The Sponsor interprets this to mean that in addition to the primary endpoint, those endpoints unrelated to OCS reduction (e.g., annual exacerbation rate) should be included in the testing hierarchy. Is this interpretation correct?

In addition, does the Agency agree that the endpoints highly correlated to the primary endpoint (i.e., endpoints which help support interpretation of OCS reduction, such as the percentage of patients who reduce their daily OCS dose completely) are not necessary for inclusion in the testing hierarchy, as they are clinically relevant (b) (4) (b) (4)

ACQ

The Sponsor wishes to thank the Agency for its recommendation to use the ACQ-7 to evaluate asthma control and the ACQ-5 to evaluate asthma symptoms in the tezepelumab program. The Sponsor agrees with the recommended approach, and has the following questions:

- Does the Agency consider the ACQ-7 to be an endpoint (b) (4) (b) (4)
- Does the Agency consider the ACQ-5 to be a separate endpoint (b) (4) (b) (4)

SGRQ

The tezepelumab program is intended to support an indication for the treatment of severe asthma patients, and only patients that meet the definition of severe asthmatics according to GINA 2017 (i.e., Steps 4-5) will be enrolled in Phase 3 studies. Recently published evidence and FDA labeling suggest that SGRQ is an appropriate tool for evaluating HRQoL/health status specifically in severe asthma patients (Nelsen, Kimel, et al., 2017; Nelson, Vernon, et al. 2017, Nucala® Package Insert). We believe SGRQ is highly relevant in the treatment of

severe asthma patients [redacted] (b) (4) Does the Agency agree?

Question 10: Assessment of Asthma Symptoms

We appreciate the Agency's response on this question and will take the feedback under advisement.

To clarify, we plan to include responder analysis of the PROs (for which there is a minimally clinically important difference) in support of the primary analysis of repeated measures analysis for mean change from baseline.

Question 11: Oral Corticosteroid Sparing Study

The Sponsor thanks the Agency for their comments and will take the feedback under advisement. We do not feel further discussion or clarification is necessary.

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

/s/

COLETTE C JACKSON
11/13/2017