

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761070Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 761070 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DPARP PDUFA Goal Date: \_\_\_\_\_ Stamp Date: 11/16/2016  
November 16, 2017

Proprietary Name: Fasenra

Established/Generic Name: benralizumab

Dosage Form: Subcutaneous; pre-filled syringe

Applicant/Sponsor: AstraZeneca AB

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_
- 

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** As an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype [DPARP comment: proposed age range is 18; DPARP plans to extend age range for approval to 12]

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**  
 No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

|                                     |         |                           | Reason (see below for further detail): |   |                                    |                                 |                          |
|-------------------------------------|---------|---------------------------|--|---|------------------------------------|---------------------------------|--------------------------|
|                                     | minimum | maximum                   | Not feasible <sup>#</sup>              | Not meaningful therapeutic benefit <sup>*</sup> | Ineffective or unsafe <sup>†</sup> | Formulation failed <sup>Δ</sup> |                          |
| <input type="checkbox"/>            | Neonate | __ wk. __ mo.             | __ wk. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> | Other   | <u>0</u> yr. <u>0</u> mo. | <u>5</u> yr. <u>11</u> mo.             | <input checked="" type="checkbox"/>             | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/>            | Other   | __ yr. __ mo.             | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/>            | Other   | __ yr. __ mo.             | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |
| <input type="checkbox"/>            | Other   | __ yr. __ mo.             | __ yr. __ mo.                          | <input type="checkbox"/>                        | <input type="checkbox"/>           | <input type="checkbox"/>        | <input type="checkbox"/> |

- Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.
- Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.**

**justification):**

## # Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

## \* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

## † Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

## Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups): |                           |               |               | Reason for Deferral                 |   |   | Applicant Certification † |
|---|---------------------------|---------------|---------------|-------------------------------------|---|---|---------------------------|
| Population                              |                           | minimum       | maximum       | Ready for Approval in Adults        | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received                  |
| <input type="checkbox"/>                | Neonate                   | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input checked="" type="checkbox"/>     | Other                     | 6 yr. 0 mo.   | 11 yr. 11 mo. | <input checked="" type="checkbox"/> | <input type="checkbox"/>                      | <input checked="" type="checkbox"/>       | <input type="checkbox"/>  |
| <input type="checkbox"/>                | Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/>                | Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/>                | Other                     | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| <input type="checkbox"/>                | All Pediatric Populations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/>            | <input type="checkbox"/>                      | <input type="checkbox"/>                  | <input type="checkbox"/>  |
| Date studies are due (mm/dd/yy): _____  |                           |               |               |                                     |   |   |                           |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: Efficacy and safety studies in adults and adolescents is completed and ready for approval and dose for 6 to 11 year olds has not yet been determined.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

| Pediatric subpopulation(s) in which studies have been completed (check below): |                              |               |               |   |                             |
|--|------------------------------|---------------|---------------|---|-----------------------------|
| Population   |                              | minimum       | maximum       | PeRC Pediatric Assessment form attached?. |                             |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input checked="" type="checkbox"/>  | Other                        | 12 yr. __ mo. | 17 yr. __ mo. | Yes <input checked="" type="checkbox"/>   | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | Yes <input type="checkbox"/>              | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: |                              |               |               |
|--|------------------------------|---------------|---------------|
| Population   |                              | minimum       | maximum       |
| <input type="checkbox"/>   | Neonate                      | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | Other                        | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/>   | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.**

*pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

| Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations: |                              |               |               |                          |                          |
|---|------------------------------|---------------|---------------|--------------------------|--------------------------|
| Population  |                              | minimum       | maximum       | Extrapolated from:       |                          |
|   |                              |               |               | Adult Studies?           | Other Pediatric Studies? |
| <input type="checkbox"/>  | Neonate                      | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | Other                        | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/>  | All Pediatric Subpopulations | 0 yr. 0 mo.   | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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COLETTE C JACKSON  
10/18/2017

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>   |                                      |  |
|--|--------------------------------------|--|
| NDA #<br>BLA # 761070  | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i>   |
| Proprietary Name: Fasenra<br>Established/Proper Name: benralizumab<br>Dosage Form: 30 mg/mL single dose pre-filled syringe   |                                      | Applicant: AstraZeneca AB<br>Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP   |
| RPM: Colette Jackson   |                                      | Division: DPARP  |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)  |                                      | <p style="margin: 0;"><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)               <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (notify CDER OND IO)</li> </ul> </li> </ul> <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions  |                                      |  |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>November 16, 2017</u></li> </ul>  |                                      | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR   |
| <ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>  |                                      | <input checked="" type="checkbox"/> None   |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____ |                                      | <input type="checkbox"/> Received  |
| ❖ Application Characteristics <sup>3</sup>   |                                      |  |

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

|  |   |
|--|---|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| ❖ Public communications ( <i>approvals only</i> )  |   |
| • Office of Executive Programs (OEP) liaison has been notified of action   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |
| • Indicate what types (if any) of information were issued  | <input checked="" type="checkbox"/> None<br><input type="checkbox"/> FDA Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |
| ❖ Exclusivity  |   |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type                                   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes   |
| ❖ Patent Information (NDAs only)   |   |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.  | <input type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.   |
| <b>CONTENTS OF ACTION PACKAGE</b>  |   |
| <b>Officer/Employee List</b>   |   |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> ) ( <a href="#">link</a> ) | <input checked="" type="checkbox"/> Included  |
| Documentation of consent/non-consent by officers/employees ( <a href="#">link</a> )  | <input checked="" type="checkbox"/> Included  |

| Action Letters   |  |
|--|--|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i>  | Action and date: Approval on November 16, 2017   |
| Labeling   |  |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>   |  |
| <ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>  | <input checked="" type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>   | <input checked="" type="checkbox"/> Included   |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>   | <input type="checkbox"/> Medication Guide<br><input checked="" type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><input type="checkbox"/> None  |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>  | <input checked="" type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>   | <input checked="" type="checkbox"/> Included   |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>   |  |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>   | <input checked="" type="checkbox"/> Included   |
| ❖ Proprietary Name   | July 28, and May 5, 2017.<br>July 27, and May 3, 2017  |
| <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>   |  |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i>  | RPM: <input type="checkbox"/> None January 26, 2017<br>DMEPA: <input type="checkbox"/> None July 17, 2017<br>DMPP/PLT (DRISK):<br><input type="checkbox"/> None July 27, and August 1, 2017<br>OPDP: <input type="checkbox"/> None July 14, 2017<br>SEALD: <input checked="" type="checkbox"/> None<br>CSS: <input checked="" type="checkbox"/> None<br>Product Quality <input type="checkbox"/> None October 5, 2017<br>Other: <input checked="" type="checkbox"/> None |
| Administrative / Regulatory Documents  |  |
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>   | January 26, 2017   |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee   | <input checked="" type="checkbox"/> Not a (b)(2)   |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>  | <input type="checkbox"/> Completed <b>(Do not include)</b>   |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> |  |
| <ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action  |
| ❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>August 2, 2017</u><br/>If PeRC review not necessary, explain: _____</li> </ul>   |   |
| ❖ Breakthrough Therapy Designation  | <input checked="" type="checkbox"/> N/A   |
| <ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>   |   |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>   |   |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>  |   |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> ) | January 5, and 27, February 9, March 10, 21, 23, 24(2), May 9, 16, and 17, June 14(2), and 21, July 13, and 20, August 1(2), 2, 18, and 23, September 14, 15, and October 5, 11, and 24 (2), 2017 |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)   | None  |
| ❖ Minutes of Meetings   |   |
| <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input checked="" type="checkbox"/> N/A or no mtg   |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>   | <input type="checkbox"/> No mtg September 20, 2016  |
| <ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input type="checkbox"/> No mtg February 13, 2013   |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>   | <input type="checkbox"/> N/A May 11, 2017   |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input type="checkbox"/> N/A August 9, 2017   |
| <ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>  |   |
| ❖ Advisory Committee Meeting(s)   | <input checked="" type="checkbox"/> No AC meeting   |
| <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>   |   |
| <b>Decisional and Summary Memos</b>   |   |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None November 6, 2017  |
| Division Director Summary Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None October 19, 2017  |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| PMR/PMC Development Templates ( <i>indicate total number</i> )  | <input type="checkbox"/> None October 30, 2017  |
| <b>Clinical</b>   |   |

|   |  |   |
|---|--|---|
| ❖ Clinical Reviews  |  |   |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> No separate review      |
| • Clinical review(s) ( <i>indicate date for each review</i> )   |  | January 12, and July 19, 2017                               |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> None                    |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )  |  | In MO review dated July 19, 2017                            |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>  |  | <input checked="" type="checkbox"/> None                    |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )  |  | <input checked="" type="checkbox"/> N/A                     |
| ❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> |  | <input checked="" type="checkbox"/> None                    |
| ❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )   |  | <input type="checkbox"/> None requested June 2, 2017        |
| <b>Clinical Microbiology</b>  |  | <input checked="" type="checkbox"/> None                    |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> No separate review                 |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None                               |
| <b>Biostatistics</b>  |  | <input type="checkbox"/> None                               |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review      |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review      |
| Statistical Review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None January 13, and July 20, 2017 |
| <b>Clinical Pharmacology</b>  |  | <input type="checkbox"/> None                               |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review      |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review      |
| Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )  |  | <input type="checkbox"/> None January 13, and July 17, 2017 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )  |  | <input checked="" type="checkbox"/> None requested          |

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

| <b>Nonclinical</b> <input type="checkbox"/> None  |   |
|---|---|
| ❖ Pharmacology/Toxicology Discipline Reviews  |   |
| • ADP/T Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> No separate review November 1, 2017  |
| • Supervisory Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> No separate review July 19, 2017   |
| • Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None January 9, and July 10, 2017  |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> No carc   |
| ❖ ECAC/CAC report/memo of meeting   | <input checked="" type="checkbox"/> None<br>Included in P/T review, page  |
| ❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )  | <input checked="" type="checkbox"/> None requested  |
| <b>Product Quality</b> <input type="checkbox"/> None  |   |
| ❖ Product Quality Discipline Reviews <sup>6</sup>   |   |
| • Tertiary review ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| • Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None January 12, July 14, and October, 2017  |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )   | <input type="checkbox"/> None Pharm/Tox- July 28, 2017 and CDRH- September 1, 2017  |
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |   |
| <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )   | October 2, 2017   |
| <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )  |   |
| <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )  |   |
| ❖ Facilities Review/Inspection  |   |
| <input type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation <b>before issuing approval letter</b> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> ) | Review dated 11/1/2017<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable |

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities  |   |
|---|---|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>   | <input type="checkbox"/> No changes<br><input type="checkbox"/> New patent/exclusivity<br><i>(Notify CDER OND IO)</i> |
| <ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>   | <input type="checkbox"/> Done   |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>  | <input type="checkbox"/> Done<br><i>(Send email to CDER OND IO)</i>   |
| ❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> | <input type="checkbox"/> Done   |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email   | <input checked="" type="checkbox"/> Done  |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter  | <input type="checkbox"/> Done   |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name                            | <input checked="" type="checkbox"/> Done  |
| ❖ Ensure Pediatric Record is accurate   | <input checked="" type="checkbox"/> Done  |
| ❖ Send approval email within one business day to CDER-APPROVALS   |   |
| ❖ Take Action Package (if in paper) down to Document Room for scanning within <b>two business days</b>  |   |

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/s/  
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COLETTE C JACKSON  
11/14/2017

BLA 761070  
Benralizumab

In your PMR/PMC correspondence via email dated October 16, 2017, you propose to conduct both PMRs under one study. While this is acceptable, we propose the following PMR language:

Conduct (b) (4) open-label, (b) (4) pharmacokinetic and pharmacodynamics study of benralizumab in pediatric patients 6 to 11 years of age with a continued safety evaluation out to (b) (4)

In order to facilitate the review of your submission, provide the requested information by October 27, 2017. You may submit your response by email to [Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Colette Jackson, Regulatory Project Manager, at 301-796-1230.

APPEARS THIS WAY ON ORIGINAL

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/s/  
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COLETTE C JACKSON  
10/24/2017

BLA 761070  
Benralizumab

Please refer to your BLA application dated November 16, 2016. We also refer to your labeling submission dated October 20, 2017. Attached are our FDA proposed revisions to your October 20, 2017, product labeling. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not the Agency's final recommendations and additional labeling changes will be forthcoming as we continue to review the labeling.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Monday, October 27, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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/s/  
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COLETTE C JACKSON  
10/24/2017

BLA 761070  
Benralizumab

Please refer to your BLA application dated November 16, 2016. We also refer to your labeling submission dated September 27, 2017. Attached are our FDA proposed revisions to your September 27, 2017, product labeling. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not the Agency's final recommendations and additional labeling changes will be forthcoming as we continue to review the labeling.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Monday, October 16, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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/s/  
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COLETTE C JACKSON  
10/11/2017

BLA 761070  
Benralizumab

We are reviewing your BLA application dated November 16, 2017. We have the following comments.

Following review of your application, we no longer agree with the studies outlined in your Agreed Pediatric Study Plan and instead request the pediatric studies listed below. Provide your commitment to conduct the following pediatric studies and provide the listed milestone dates for each of the studies listed below.

PMR # 1            Conduct (b) (4) open-label, pharmacokinetic and pharmacodynamics study of benralizumab in pediatric patients with (b) (4) 6 to 11 years of age

|                                 |   |
|---------------------------------|---|
| Draft protocol submission date  | <b>Insert Date</b>  |
| Final protocol submission date: | <b>Insert Date</b>  |
| Study completion date:          | <b>Insert Date</b>  |
| Final report submission date:   | <b>Insert Date (This date should be the same for both PMR #1 and PMR#2)</b> |

PMR # 2

(b) (4)

|                                 |   |
|---------------------------------|---|
| Draft protocol submission date: | <b>Insert Date</b>  |
| Final protocol submission date: | <b>Insert Date</b>  |
| Study completion date:          | <b>Insert Date</b>  |
| Final report submission date:   | <b>Insert Date (This date should be the same for both PMR #1 and PMR#2)</b> |

Provide your commitment to conduct the following and provide the final report submission date.

PMC #1            Perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Perform testing at regular intervals and include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Update study results in the BLA Annual Report. Submit the complete data and risk evaluation for potential impact of leachables on product safety and quality to the BLA.

Final Report Submission Date: **Insert Date**

In order to facilitate the review of your submission, provide the requested information by October 17, 2017. You may submit your response by email to Colette.Jackson@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Colette Jackson, Regulatory Project Manager, at 301-796-1230.

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/s/  
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COLETTE C JACKSON  
10/05/2017

BLA 761070  
Benralizumab

Please refer to your BLA application dated November 16, 2016. We also refer to your labeling submission dated August 2, 2017. Attached are our FDA proposed revisions to your August 2, 2017, product labeling. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not the Agency's final recommendations and additional labeling changes will be forthcoming as we continue to review the labeling.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Thursday, September 21, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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

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/s/  
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COLETTE C JACKSON  
09/15/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB September 25, 2017 in order to continue our evaluation of your application.

Regarding the September 1, 2017 response to Question 1 of the August 18, 2017 information request:

1. As was indicated in your response, the particle standards utilized in the visible particles method (b) (4)

[Redacted]

[Redacted] (b) (4)



If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 9/14/2017 08:20:13AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1



BLA 761070  
Benralizumab

Please refer to your BLA application dated November 16, 2016. We also refer to your submission dated August 11, 2017. We have the following labeling comments. Be advised that these labeling comments are not the Agency's final recommendations and additional labeling changes and comments will be forthcoming as we continue to review the labeling.

**A. Lidding Labeling (Commercial and Professional Sample)**

1. The Agency does not consider the lidding labeling a partial label since the partial label regulation pertains to container labels [see 21 CFR 610.60 (c)]. "No preservative" is required information per 21 CFR 610.61 (e). To accommodate the addition of this information, consider locating the statement to appear on the line after the "Do not shake or freeze." statement.
2. "No U.S. standard of potency" is required information per 21CFR 610.61 (r). This can be added to the lidding labeling as follows:

"Do not shake or freeze the syringe.  
No Preservative. No U.S. Standard of Potency"

3. We agree with the consideration for space regarding the listing of inactive ingredients on the lidding labeling. We note the appearance of this information on the carton labeling and in the prescribing information.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Wednesday, August 30, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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/s/  
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COLETTE C JACKSON  
08/23/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

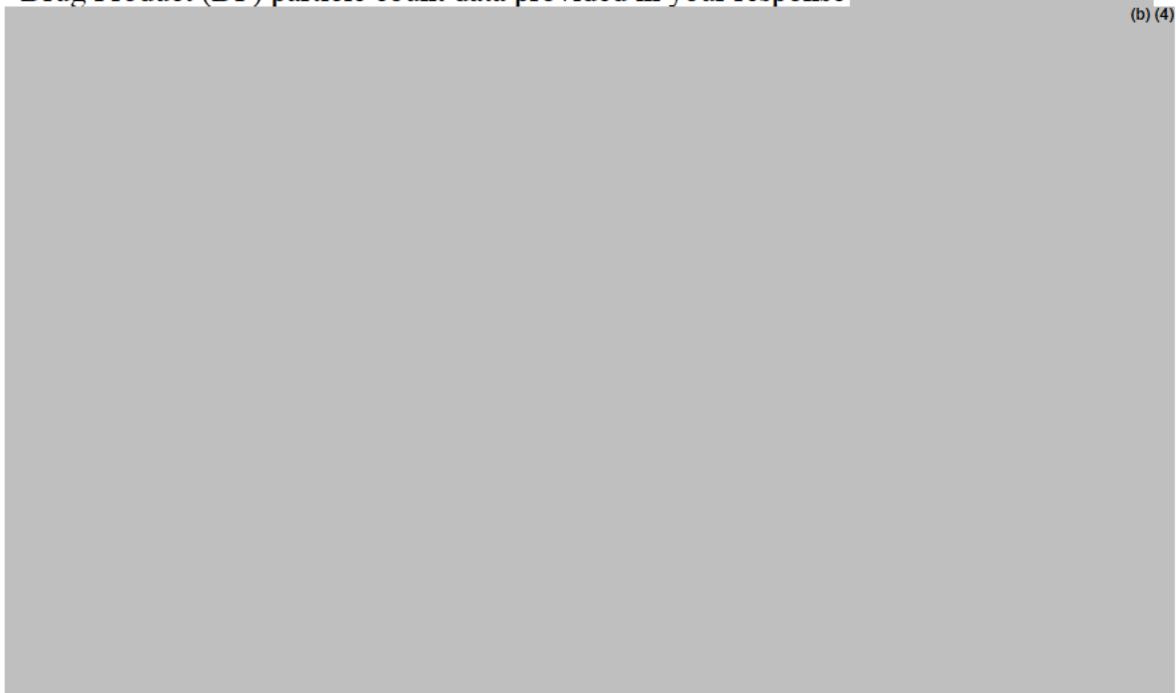
Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB August 25, 2017 in order to continue our evaluation of your application.

Regarding the responses to the information request communicated on July 13, 2017 (responses received August 11, 2017):

1. Regarding your response to Question 3: The Drug Substance (DS), <sup>(b) (4)</sup> and Drug Product (DP) particle count data provided in your response <sup>(b) (4)</sup>



(b) (4)

2. (b) (4)

- a. (b) (4)
- b. (b) (4)

(b) (4)

3. Regarding your response to Question 22b: After an action is taken, the extension of the shelf life for benralizumab DP should be based on real time data. The DP shelf life can be extended to (b) (4) months based on acceptable (b) (4) month time point data, and the shelf life can be extended to (b) (4) months based on acceptable (b) (4) month time point data. Update the DP stability section (3.2.P.8.2; Table P.8.2-1) to state that shelf life extensions will only be made after the appropriate data have been obtained.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 8/18/2017 10:44:27AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1





BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB August 16, 2017 in order to continue our evaluation of your application.

1. In your application you have provided functional performance tests for the accessorized prefilled syringe (APFS). You also state that you have followed the FDA guidance document, Medical Devices with Sharps Injury Prevention Features and ISO Standard 23908. I was unable to locate the performance test reports for the APFS sharps injury prevention feature. In the FDA guidance document it recommends using 500 samples with zero failures for acceptable results. Please provide the completed test reports for the sharps injury prevention for our review. This information is necessary to ensure the APFS in BLA 761070 will protect the health care provider from accidental needle stick injuries.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 8/02/2017 11:13:34AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1



BLA 761070  
Benralizumab

We are reviewing your BLA application dated November 16, 2016, and we have the following request for additional information.

Submit your statistical analysis programs for generating summary statistics of demographics and baseline characteristics used in Table 2 of your proposed labeling. Please provide program codes with sufficient detail so that we may understand how you used the flag variables and records included in your analysis datasets for these analyses.

Please provide a response to the request by email ([Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov)) by COB Friday, August 4, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

APPEARS THIS WAY ON ORIGINAL

Drafted: August 1, 2017

Initialed: Jade Wang/ August 1, 2017  
Yongman Kim/ August 1, 2017

Finalized: CCJ/ August 1, 2017

Filename: 761070 August 2017 Stats fax.doc

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/s/  
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COLETTE C JACKSON  
08/01/2017

BLA 761070  
Benralizumab

We are reviewing your BLA application dated November 16, 2016. We have the following comments regarding your proposed container and carton labeling. Be advised that these labeling changes are not the Agency's final recommendations and additional labeling changes will be forthcoming as we continue to review the labeling.

#### **A. General Comments**

1. FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying a decision on the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.
2. Please refer to our July 28, 2017, Proprietary Name Request Conditionally Acceptable letter. Replace the placeholder "Tradename" throughout the PI and all the commercial and professional sample carton labels, lidding labels, and syringe labels with the conditionally acceptable proprietary name and resubmit.

#### **B. Prefilled Syringe Label (Commercial and Professional Sample)**

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name by using bold typeface in accordance with 21 CFR 201.10(g)(2).
2. Unbold and reduce prominence of "Rx Only" to allow for prominence of other critical information on the Principal display panel (PDP).
3. Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21CFR 610.60(a)(2). Revise from "AstraZeneca" to read "AstraZeneca AB"

#### **C. Lidding and Carton Labeling (Commercial and Professional Sample)**

1. Ensure the licensed manufacturer appears as the listed Applicant on the submitted Form FDA 356h per 21 CFR 610.61. Revise from (b) (4) to read "Manufactured by: AstraZeneca AB"

Sodertalje, Stockholm County Sweden SE-15185  
US License No. XXXX”

Remove the word (b) (4) from the US license No. statement.

You may include the distributor name and address on the lidding and carton labeling if you have fulfilled 21 CFR 610.61 as above. The distributor should appear as: “Distributed by: Distributor name and address”

2. Ensure “No preservative” appears on the lidding labeling per 21 CFR 610.61(e).
3. Revise the storage statement from (b) (4) to read **“Store the prefilled syringe refrigerated at 2°C - 8°C (36°F - 46°F) in original carton to protect from light. Do not shake or freeze the syringe.”** We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
4. Revise the inactive ingredients list from (b) (4) to read “Contents: One 1-mL single-dose prefilled syringe that delivers 30 mg benralizumab, L-histidine... and Water for Injection, USP.” Ensure that the inactive ingredients appear in alphabetical order per USP <1091> Labeling of Inactive Ingredients.  
  
Add the list of inactive ingredients to the lidding labeling. To accommodate this addition, remove the trademark statement, as the trademark statement is not required information per 21 CFR 201.15.
5. On the lidding, add the words “No U.S. standard of potency” per 21CFR 610.61 (f).
6. Relocate and revise the discard statement to appear adjacent to the package type term as follows: “1 single-dose prefilled syringe. Discard unused portion.”
7. On the carton labeling, revise the usual dose statement from (b) (4) to read “Usual Dosage: See prescribing information” per 21 CFR 201.55.

#### **D. Professional Sample Carton Label**

1. Revise the statement “PROFESSIONAL SAMPLE – NOT FOR SALE” with bold typography to emphasize this important information

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Tuesday, August 8, 2017. Your response must also be submitted formally to your BLA application

shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: August 1, 2017

Initialed: Sofia Chaudhry/ July 31, 2017  
Lydia Gilbert-McClain/ July 31, 2017

Finalized: CCJ/ August 1, 2017

Filename: 761070 August 2017 CC Label fax.doc

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/s/  
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COLETTE C JACKSON  
08/01/2017



BLA 761070

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

AztraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

ATTENTION: Les Thomas  
Director, Global Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab, 30 mg/mL.

We also refer to your correspondence, dated and received May 18, 2017, requesting review of your proposed proprietary name, Fasentra.

We have completed our review of the proposed proprietary name, Fasentra and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 18, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
07/28/2017

BLA 761070  
Benralizumab

We are reviewing your BLA application dated November 16, 2016. Attached are our revisions to your proposed package insert (PI). The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not the Agency's final recommendations and additional labeling changes will be forthcoming as we continue to review the labeling.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes by email (Colette.Jackson@fda.hhs.gov) by COB Friday, July 28, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosure: FDA Proposed Labeling (annotated and clean)

42 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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COLETTE C JACKSON  
07/20/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information.

Regarding the responses to previous information requests:

1.



2. The June 30, 2017 response to question 26 is not acceptable. Color and clarity are key indicators of product acceptability and ensure that the material is satisfactory for future manufacture into (b) (4) DP that will pass release testing. Implement color and clarity as part of DS release and stability testing. See Comment 16, below, regarding the acceptance criteria for these quality attributes.
3. There is insufficient justification for the proposed (b) (4) acceptance criteria for DS, (b) (4) and DP. The release and stability results presented state that all lots have been free or practically free from visible particles, and the batch release results for all Process 3 Clinical lots were free from visible particles. In

addition, your June 30, 2017 response to question 27 states that “the occurrence of inherent, visible particles in benralizumab has been low.” However, SOPs QC-040620 (DS, (b) (4)) and QC-040701 (DP) state that the limit for this assay is “< Particle Standard (b) (4)” which corresponds to a particle count of (b) (4) particles/mL. Therefore, it appears that the proposed limit represents a visible particle level that has not been experienced with benralizumab. Tighten the acceptance criteria to reflect a specific limit justified by your clinical and manufacturing experience, and provide raw data to support the proposed acceptance criteria.

4. The proposed acceptance criteria for charge variants for DS, (b) (4) and DP lot release and stability are not acceptable, (b) (4)



5. Regarding reference standards (RS) and the June 30, 2017 response to question 30:

- a.



(b) (4)

- b. It is not clear that the updates to the “conforms to reference” criteria to include the definition of conformance provide useful requirements. (b) (4)

(b) (4)

however, no consistency in the relative amounts of variants detected using these assays was included. Justify the value of these criteria with respect to ensuring that benralizumab remain consistent over its lifecycle or update the criteria to include appropriate requirements.

- c. (b) (4)

6. (b) (4)

7. (b) (4)

c.

(b) (4)

d.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 7/13/2017 11:25:50AM  
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BLA 761070  
Benralizumab

We are reviewing your BLA application dated November 16, 2016, and we have the following request for additional information.

Provide reports for the studies listed below.

1. Forced extraction studies of the three separate components of the (b) (4) 1 mL long syringes ( (b) (4) elastomeric needle shield, (b) (4) plunger stopper, Type I (b) (4) glass barrel with 29-gauge (b) (4) needle), and the syringe tip (b) (4) stainless steel needle adhered to the glass tip of the syringe).
2. Simulation study with the (b) (4) syringes filled with 1.0 mL of Drug Product (b) (4) (20 mM histidine/histidine-HCl, 250 mM trehalose dihydrate, 0.006% w/v PS-20, pH 6.0).
3. Leachables studies with three lots of Drug Product (Lots 020F15, 021F15, and 004K15).

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Monday, July 10, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: July 3, 2017

Initialed: Timothy Robison/ July 3, 2017  
Carol Galvis/ July 3, 2017

Finalized: CCJ/ July 3, 2017

Filename: 761070 July 2017 PT fax.doc

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/s/  
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COLETTE C JACKSON  
07/03/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB June 29, 2017 in order to continue our evaluation of your application.

**Section 3.2.S.2.2, Description of Manufacturing Process and Process Controls**

- 1.
- 2.
- 3.
- 4.
- 5.



6.  (b) (4)

**Section 3.2.S.2.4, Control of Critical Steps and Intermediates**

7. Provide bioburden and endotoxin action limits in section 3.2.S.2.4 of the BLA.

**Section 3.2.S.2.5, Process Validation**

8.  (b) (4)

9.

10.

11.

12.

**Section 3.2.S.4.2, Analytical Procedures**

13.  (b) (4)

14.

(b) (4)

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 6/21/2017 11:18:15AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1



BLA 761070  
Benralizumab

We are reviewing the financial disclosure information included in your BLA application dated November 16, 2016, and the updated information included in your May 9, 2017, submission. We have the following request for additional information.

Provide the total number of investigators and sub-investigators in each of following studies: D3250C00017, D3250C00018, D3250C00020, D3250C00029, D3250C00032 and MI-CP220.

Please provide a response to the request by email ([Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov)) by COB Wednesday, June 21, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: June 14, 2017

Initialed: Sofia Chaudhry/ June 13, 2017  
Lydia Gilbert-McClain/ June 13, 2017

Finalized: CCJ/ June 14, 2017

Filename: 761070 June 2017 MO fax.doc

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/s/  
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COLETTE C JACKSON  
06/14/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB June 23, 2017 in order to continue our evaluation of your application.

Regarding Section 3.2.S.2.2:

1.

2.

(b) (4)

46.

(b) (4)

47. Update Section 3.2.P.8 with all available stability data for the Process C Commercial DP batches to support setting a DP expiry period.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 6/14/2017 10:27:58AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1





BLA 761070

**PROPRIETARY NAME  
ACKNOWLEDGEMENT**

AztraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

ATTENTION: Les Thomas  
Director, Global Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab, 30 mg/mL.

We acknowledge receipt of your correspondence, dated and received May 18, 2017, requesting a reconsideration of your proposed proprietary name, Fasenra.

The user fee goal date will be August 16, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Neil Vora, PharmD, MBA, PMP  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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NEIL VORA  
06/02/2017

BLA 761070  
Benralizumab

We are reviewing your BLA submission dated November 16, 2016, and we have the following comments and requests for information.

1. We see 3 cases of lymphoma reported in your 120-day safety update submitted on March 16, 2017 (PT ID: E0311502, E1001501, E2622504). Provide case narratives for these patients and your assessment for the risk of lymphoma with the use of benralizumab.
2. In the 5.3.5.3 integrated safety report you reference use of a modified hypersensitivity SMQ. Clarify how the SMQ was modified, including what terms were included and those removed to create the modification. If this is already contained in the application, provide the location for the information.

Please provide a response to the request by email ([Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov)) by COB Wednesday, May 31, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: May 17, 2017

Initialed: Sofia Chaudhry/ May 16, 2017  
Lydia Gilbert-McClain/ March 16, 2017

Finalized: CCJ/ March 17, 2017

Filename: 761070 May 2017 MO fax.doc

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/s/  
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COLETTE C JACKSON  
05/17/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB May 25, 2017 in order to continue our evaluation of your application.

1.

2.

(b) (4)

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

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BLA 761070

**MID-CYCLE COMMUNICATION**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
Wilmington, Delaware 19803

Attention: Les Thomas  
Director, Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab 30 mg/mL injection solution.

We also refer to the teleconference between representatives of your firm and the FDA on May 11, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

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: Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** May 11, 2017, from 3:30 PM to 4:30 PM EST

**Application Number:** BLA 761070  
**Product Name:** Benralizumab  
**Indication:** Asthma  
**Applicant Name:** AstraZeneca AB

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

**FDA ATTENDEES**

**Division of Pulmonary, Allergy, and Rheumatology Products**

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Lydia Gilbert-McClain, Deputy Division Director  
Sofia Chaudhry, M.D., Medical Officer  
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader  
Carol Galvis, Ph.D., Acting Pharmacology/Toxicology Team Leader  
Colette Jackson, Senior Regulatory Health Project Manager

**Office of Biostatistics**

Shanti Gomatam, Ph.D., Acting Statistical Team Leader  
Yu (Jade) Wang, Ph.D., Statistical Reviewer

**Office of Clinical Pharmacology**

Ping Ji, Ph.D., Biologics Team Leader  
Sury Sista, Ph.D., Clinical Pharmacology Reviewer  
Yunzhao Ren, Ph.D., Clinical Pharmacology Reviewer

**Division of Risk Management**

Charlotte Jones, M.D., Risk Management Analyst/ Medical Officer

**ASTRAZENECA AB ATTENDEES**

Colin Reisner, M.D., VP, Respiratory Global Medicines  
Mark White, M.D., Global Medicine Leader  
Mitch Goldman, M.D., Ph.D., Global Clinical Leader  
Peter Barker, Ph.D., Global Product Statistician  
Sherahe Fitzpatrick, M.D., Global Safety Physician, Patient Safety

Milt Axley, Ph.D., Global CMC Team Leader  
Paul Newbold, Ph.D., Fellow, Translational Sciences  
Fadi Hakki, CMC Regulatory Lead  
Scott Manetz, Ph.D., Fellow, Toxicologist  
Les Thomas, Global Regulatory Lead  
Azin Shahzamani, VP, Regulatory Affairs

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT ISSUES

*We note that your clinical development program includes data on 108 adolescents age 12 to 17 and acknowledge your requests for a partial waiver and deferral of pediatric studies in children (b) (4) and age (b) (4) to 11 years old respectively. The handling of the adolescent data in the prescribing information and the required pediatric assessments for benralizumab remain a review issue.*

### **Meeting Discussion:**

AstraZeneca (AZ) asked if FDA has completed review of the data sets. The FDA informed AZ that the review is still ongoing.

AZ referred to the 74 day filing communication comment regarding the loading dose and asked the FDA if there are any updates on this issue. The FDA stated the review is ongoing and there have been no issues identified for discussion.

## 3.0 INFORMATION REQUESTS

*There are no outstanding information requests. Additional information requests will be sent if necessary to assist in the review of your application.*

### **Meeting Discussion:**

No discussion held for this comment.

#### **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

*No major safety concerns have been identified at this time.*

**Meeting Discussion:**

No discussion held for this comment.

#### **5.0 RISK MANAGEMENT UPDATE**

*Based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.*

**Meeting Discussion:**

No discussion held for this comment.

#### **6.0 ADVISORY COMMITTEE MEETING**

*There are no plans for an advisory committee meeting at this time.*

**Meeting Discussion:**

AZ asked the FDA to confirm that an AC will not be held for his application. The FDA confirmed that an AC is not being planned for this application.

#### **7.0 LATE-CYCLE MEETING**

*August 9, 2017; Face to Face Meeting*

**Meeting Discussion:**

AZ asked the FDA to outline the milestone timelines for this application. The FDA stated this will be provided post meeting via email. The FDA provided the timelines in an email dated May 11, 2017.

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/s/  
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COLETTE C JACKSON  
05/30/2017

# **PDUFA V Program Mid-Cycle Communication Agenda**

## **BLA 761070 Benralizumab**

**Teleconference**

**May 11, 2017**

**3:30 PM – 4:30 PM EST**

**1. AstraZeneca/FDA Review Team/ERG Independent Assessor Introductions**

**2. Introductory Comments**

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

**3. Significant Review Issues**

We note that your clinical development program includes data on 108 adolescents age 12 to 17 and acknowledge your requests for a partial waiver and deferral of pediatric studies in children (b) (4) and age (b) (4) o 11 years old respectively. The handling of the adolescent data in the prescribing information and the required pediatric assessments for benralizumab remain a review issue.

**4. Information Requests**

There are no outstanding information requests. Additional information requests will be sent if necessary to assist in the review of your application.

**5. Major Safety Concerns**

No major safety concerns have been identified at this time.

**6. Risk Management Update**

We do not anticipate a REMS for this application at this time.

7. **Advisory Committee Meeting Plans**

There are no plans for an advisory committee meeting at this time.

8. **Date and Format for Late-Cycle Meeting**

August 9, 2017; Face to Face Meeting

Drafted: May 8, 2017

Initialed: Jackson for Barnes/ May 8, 2017  
Sofia Chaudhry/ May 8, 2017  
Lydia Gilbert-McClain/ May 8, 2017  
Badrul Chowdhury/ May 9, 2017

Finalized: CCJ/ May 9, 2017

Filename: 761070 May 2017 MC Agenda fax.doc

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/s/  
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COLETTE C JACKSON  
05/09/2017



BLA 761070

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

AztraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

ATTENTION: Les Thomas  
Director, Global Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab, 30 mg/mL.

We also refer to your correspondence, dated and received February 7, 2017, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

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We note that you have proposed an alternate proprietary name in your submission dated February 7, 2017. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Colette Jackson, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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DANIELLE M HARRIS on behalf of TODD D BRIDGES  
05/05/2017

BLA 761070  
Benralizumab

We are reviewing your BLA submission dated November 16, 2016, and we have the following comment and request for information.

We note a trend for an increased number of WBC counts with low grade lymphopenia (Grade 1 per CTCAE criteria) in the active treatment arms compared to placebo in the SIROCCO and CALIMA studies. Provide a tabulation of the number of patients in each treatment arm with a low lymphocyte count per CTCAE grade (Grade 1, 2, 3, and 4) obtained on-treatment. In addition provide a graphical representation of the lymphocyte counts over time for each patient identified to have a low lymphocyte count in these studies.

Please provide a response to the request by email ([Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov)) by COB Friday, April 7, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: March 24, 2017

Initialed: Barnes/ March 24, 2017

Sofia Chaudhry/ March 23, 2017

Lydia Gilbert-McClain/ March 23, 2017

Finalized: CCJ/ March 24, 2017

Filename: 761070 March 2017 MO fax.doc

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/s/  
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COLETTE C JACKSON  
03/24/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB April 4, 2017 in order to continue our evaluation of your application.

1. Please provide an updated manufacturing schedule for benralizumab drug substance at the Frederick Manufacturing Center, Frederick, MD including details on the (b) (4) [REDACTED] for the campaign scheduled in April-June 2017.

If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 3/24/2017 07:37:43AM  
GUID: 57e29be6020b38ae4817a9d8118b31c1



BLA 761070  
Benralizumab

We are reviewing your BLA submission dated November 16, 2016, and we have the following comments and requests for information.

You listed blood eosinophil counts in RSLB.xpt from Studies D3250C00017 and D3250C00018. The results on Week 56 (Study D3250C00017) and Week 60 (Study D3250C00018) showed that the mean blood eosinophil counts returned to approximately 100 cells/ $\mu$ L and 150 cells/ $\mu$ L after 4 weeks and 8 weeks from the last dose of Q8W dosing regimen. The results are consistent with Study MI-CP197 [blood eosinophil count on Day 112 (8 weeks after last 25 mg dose) in Figure 11.5 on page 709 of CSR MI-CP197] and Study MI-CP220 [blood eosinophil count on Week 52 (12 weeks after last 20 mg dose) in Figure 11.4.1.3-2 on page 141 of CSR MI-CP220].

However, the fluctuation of mean blood eosinophil counts were not adequately reflected in time points within the treatment duration (Figure 16 on page 174 of from Studies D3250C00017 and Figure 17 on page 176 from Studies D3250C00018). Based on the fast action of benralizumab, the blood eosinophil counts are expected to be dramatically different before and after the dose. Therefore, provide blood eosinophil tables extracted from RSLB.xpt (one table from Study 17 and one table from Study 18) including the following key columns: STUDYID, USUBJID, TRTA, AVISIT, PARAM (include Eosinophils\_Central or Eosinophils\_Local), AVAL, BASE, CHG, and RTIME

RTIME is defined as relative time [unit as Day] before or after the exact dosing time of that visit.

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Thursday, March 29, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: March 22, 2017

Initialed: Barnes/ March 22, 2017  
Ren/ March 21, 2017  
Marathe/ March 21, 2017

Finalized: CCJ/ March 23, 2017

Filename: 761070 March 2017 CP fax no 2.doc

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/s/  
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COLETTE C JACKSON  
03/23/2017



BLA 761070

**INFORMATION REQUEST**

AstraZeneca AB  
Attention: Les Thomas  
Director, Regulatory Affairs  
4222 Emperor Blvd, Suite 560  
Durham, NC 27703

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for benralizumab.

We are reviewing your submission and have the following requests for information. We request a prompt written response by COB April 4, 2017 in order to continue our evaluation of your application.

1. Regarding the description of your drug substance manufacturing process in Section 3.2.S.2.2, provide the following pieces of additional information:

a)

b)

c)

d)

(b) (4)



If you have questions, call me, at (301) 348-3054.

Sincerely,

*{See appended electronic signature page}*

Kelly Ballard, MS  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Kelly  
Ballard

Digitally signed by Kelly Ballard  
Date: 3/21/2017 01:23:48PM  
GUID: 57e29be6020b38ae4817a9d8118b31c1



BLA 761070  
Benralizumab

We are reviewing your BLA submission dated November 16, 2016, and we have the following comments and requests for information regarding your February 28, 2017, submission.

1. We acknowledge the simulation results provided in your response and it is consistent with the conclusion from your population PK model that the relative bioavailability is approximately 15% lower from the process 2 formulation compared to the process 3 formulation. The impact of this on labeling in section 12 will be a review issue.
2. We acknowledge that your exposure response analysis on asthma exacerbation rate was stratified by dosing regimens in Figure 16 on page 60 of your exp-resp-modeling-report.pdf. Clarify if the  $C_{\text{trough}}$  in Figure 16 is model-predicted  $C_{\text{trough}}$ , but not observed  $C_{\text{trough}}$ . In addition, provide an exacerbation rate ratio- $C_{\text{trough}}$  plot with the pooled data from the two dosing regimens (Q4W  $\times$ 3 +Q8W and Q4W).
3. There were 5 patients in 30 mg Q8W from Study D3250c00017 who received incorrect study treatment. Provide detailed dosing information on these 5 patients. Clarify if the dosing information of those 5 patients were corrected in your population PK dataset. In addition, clarify if similar incorrect treatment occurred in Study D3250c00018 as well.

Please provide a response to the request by email (Colette.Jackson@fda.hhs.gov) by COB Friday, March 17, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: March 7, 2017

Initialed: Barnes/ March 7, 2017  
Ren/ March 6, 2017  
Marathe/ March 6, 2017

Finalized: CCJ/ March 17, 2017

Filename: 761070 March 2017 CP fax.doc

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COLETTE C JACKSON  
03/10/2017

BLA 761070  
Benralizumab

We are reviewing your BLA submission dated November 16, 2016, and we have the following comments and requests for information.

It appears that at least four different formulations were developed and used in various benralizumab clinical studies. Different formulations developed for subcutaneous injection sometimes resulted in different bioavailability and PK profiles. It appears that there were no PK-bridging studies or justifications submitted to support that the pharmacokinetics and pharmacodynamics results obtained from early formulations could be applied to the to-be-marketed formulations. (b) (4)

Please provide the following:

- A summary table of different formulations used in each of benralizumab clinical study.
- A thorough justification supporting the cross-formulation extrapolation.
- A clarification if formulation was evaluated as a covariate in your population PK analysis.

Provision of reasonable justifications will aid in retaining the drug information that are not from the to-be-marketed formulation in the label.

Please provide a response to the request by email ([Colette.Jackson@fda.hhs.gov](mailto:Colette.Jackson@fda.hhs.gov)) by COB Thursday, February 23, 2017. Your response must also be submitted formally to your BLA application shortly thereafter. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: February 9, 2017

Initialed: Barnes/ February 9, 2017  
Ren/ February 8, 2017  
Marathe/ February 8, 2017

Finalized: CCJ/ February 9, 2017

Filename: 21929 s013 CP Oct 2016 fax.doc

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COLETTE C JACKSON  
02/09/2017



BLA 761070

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
Wilmington, Delaware 19803

Attention: Les Thomas  
Director, Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab 30 mg/mL injection solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 16, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 28, 2017. This date conforms to the 21<sup>st</sup> Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is April 27, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

**CLINICAL**

1. The impact and necessity of your proposed benralizumab 30 mg Q4week x 3 loading dose will be a review issue.
2. Given the importance of patient reported outcomes, the ACQ and AQLQ results are of particular interest. Whether to include these results into the product labeling will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We have the following comments and requests for information:

1. Provide the following tabulations of exposure-adjusted treatment emergent adverse events and treatment emergent serious adverse event using pooled safety data from Trials MI-CP220, SIROCCO, CALIMA, ZONDA and BISE.

|                    | 2 mgQ4                 |                             | 20 mg x Q4             |                             | 30 mg Q4 x 3<br>30 mg Q8 |                             | 30 mg Q4               |                             | 100 mg Q4              |                             |
|--------------------|------------------------|-----------------------------|------------------------|-----------------------------|--------------------------|-----------------------------|------------------------|-----------------------------|------------------------|-----------------------------|
|                    | Number (%) of patients | Event rate per 100 pt years | Number (%) of patients | Event rate per 100 pt years | Number (%) of patients   | Event rate per 100 pt years | Number (%) of patients | Event rate per 100 pt years | Number (%) of patients | Event rate per 100 pt years |
| System Organ Class |                        |                             |                        |                             |                          |                             |                        |                             |                        |                             |
| Preferred Term     |                        |                             |                        |                             |                          |                             |                        |                             |                        |                             |

2. According to the Reviewer’s guide in the datasets folder for the Exposure-Response Modeling report (Module 5.3.3.5), “The datasets for population PK and exposure analysis materials reside in datasets folder while the corresponding NONMEM output files, SAS output files, and SPlus scripts are stored under Programs”. We located the NONMEM code for the Pop PK analysis in the Exposure-Response Modeling report directory. However, we could not locate a “Programs” subdirectory and NONMEM output files, SAS output files, and SPlus scripts in this folder. For the population PK report, submit (a) control stream files, and any datasets that were used in the NONMEM run for Pop PK

analysis but NOT already included in the Exposure-Response Modeling report directory (including .xpt and ASCII); (b) S-Plus or R-Scripts and datasets, if any.

The following are the general expectations for submitting the pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a 'define.pdf' file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.
- For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a 'define pdf' file to explain the role of each file and sometimes with a pdf file as the 'revieweraid.pdf' to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a 'define pdf' file to explain the variables within each data file.

3. You note that your blinded sample size re-estimation analysis was "performed by AstraZeneca internal personnel or it designees." Please clarify who performed the analysis and who had access to the data, what procedures were in place to keep sponsor personnel blinded to comparative interim results, and what were the detailed results from the interim analysis. Submit minutes from any interim monitoring meetings, including meetings to discuss the interim analysis results.
4. We note in your BLA submission that you provided a summary of your preliminary analyses and evaluations, including formative studies and your intend-to-market labels and labeling. However, we note that the following items were not provided in your BLA submission:

- An updated use related-risk analysis for your product;
- Detailed HF validation study report. See Appendix A of Guidance Applying Human Factors and Usability Engineering to Medical Devices, available online at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf> for a description of elements to include in the HF validation study report.
- Five intend-to-market samples of product
- Summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the human factors validation study, including a description of how the changes were validated;

○

(b) (4)

Please respond only to the above requests for information by COB January 31, 2017. Additionally, please note that Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study reports and related information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

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

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert and Patient Information sheet.

Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert and patient information sheet and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
01/27/2017



BLA 761070

**BLA ACKNOWLEDGMENT**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
Wilmington, Delaware 19803

Attention: Les Thomas  
Director, Regulatory Affairs

Dear Mr. Thomas:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Benralizumab  
Date of Application: November 16, 2016  
Date of Receipt: November 16, 2016  
Our Reference Number: BLA 761070

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2017, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

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

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/s/  
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COLETTE C JACKSON  
01/05/2017



IND 100237

**MEETING MINUTES**

MedImmune  
One MedImmune Way  
Gaithersburg, Maryland 20878

Attention: Steve Danielson  
Senior Director, Global Regulatory Affairs

Dear Mr. Danielson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for benralizumab (MEDI-563).

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2016. The purpose of the meeting was to discuss the proposed overall content and format of data from Phase 3 clinical trials to be submitted in the BLA for an indication of add-on treatment for (b) (4) asthma with eosinophilic inflammation in adults and adolescents 12 years of age and older.

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

If you have any questions, call 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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** September 20, 2016, from 3:30 PM to 5 PM EST  
**Meeting Location:** White Oak Building 22, Conference Room 1309

**Application Number:** IND 100237  
**Product Name:** benralizumab (MEDI-563)  
**Indication:** Asthma  
**Sponsor/Applicant Name:** MedImmune

**Meeting Chair:** Lydia Gilbert-McClain, M.D.  
**Meeting Recorder:** Colette Jackson

**FDA Attendees:**

**Division of Pulmonary, Allergy, and Rheumatology Products**

Lydia Gilbert-McClain, M.D., Deputy Division Director  
Sofia Chaudhry, M.D., Clinical Reviewer  
Colette Jackson, Senior Regulatory Health Project Manager  
Susan Rhee, Pharm. D., Project Management Officer

**Office of Biostatistics**

Lan Zeng, M.S., Statistical Reviewer

**Office of Biotechnology Products**

Sarah Kennett, Ph.D., Review Chief

**Office of Clinical Pharmacology**

Dipak Pisal, Ph.D., Clinical Pharmacology Reviewer  
Anshu Marathe, Ph.D., Clinical Pharmacology Team Leader  
Robert Schuck, Ph.D., Clinical Pharmacology Reviewer

**Office of Surveillance and Epidemiology**

Michael Sinks, Pharm.D., Regulatory Project Manager

**Sponsor Attendees:**

**MedImmune**

Colin Reisner, M.D., Vice President, Clinical, Respiratory  
Mark White, M.D., Global Medicine Leader  
Mitch Goldman, M.D., Ph.D., Global Clinical Leader  
Peter Barker, Ph.D., Global Product Statistician  
Steve Danielson, Global Regulatory Lead  
Azin Shahzamani, Vice President, Regulatory Affairs  
Li Li, MD, Ph.D., Lead Regulatory Project Manager  
Mayur Patel, Pharm.D., Vice President, Patient Safety

**1.0 BACKGROUND**

MedImmune sent in a Pre-BLA meeting request dated June 8, 2016, to discuss their proposed overall content and format of data from Phase 3 clinical trials to be submitted in the BLA for an indication of add-on treatment for (b) (4) asthma with eosinophilic inflammation in adults and adolescents 12 years of age and older. The briefing package was received on August 15, 2016. Upon review of the briefing package, the FDA sent Preliminary Comments to MedImmune on September 15, 2016. The content of that communication is printed below. On September 19, 2016, MedImmune outlined their discussion points via email in a clarification document to facilitate the discussion. This was officially submitted on September 20, 2016, 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**

***Chemistry, Manufacturing, and Controls***

***Question 1: Does the Agency agree that Prior Approval Inspection of FMC for benralizumab can occur during the active production period of any platform process campaign?***

**FDA Response:**

*We do not agree. For a Pre-License Inspection, the Agency expects that the product under review will be manufactured at the Drug Substance manufacturing facility. We do not agree that a non-product specific inspection of the FMC during any active production period of a platform process Drug Substance can meet the requirements of a PAI. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. Preliminary manufacturing schedules should be provided in Module 1 of the application to facilitate planning of pre-license inspections. The application should include a complete list of the manufacturing and testing sites with their corresponding FEI numbers.*

**DISCUSSION:**

There was no discussion held for this response.

***Question 2: It is requested the Agency provide a draft AstraZeneca AB Biologic License Number 30 days prior to the action or approval date to decrease the wait time for patient access to benralizumab – Does the Agency agree?***

**FDA Response:**

*A pending US license number is assigned upon receipt of a new BLA. This pending number will be included in all FDA draft labeling during labeling negotiations to ensure the labeling contains this required information. Once the BLA is approved, the license number will be granted and is listed in the approval letter. If the BLA is not approved, the US license number remains pending.*

**DISCUSSION:**

There was no discussion held for this response.

***Clinical***

***Question 3: Does the Agency agree that the body of evidence proposed to be included in the benralizumab BLA is sufficient to inform an assessment of the benefit:risk profile for the proposed indicated population?***

**FDA Response:**

*We agree that your data are sufficient to file a BLA application. We note your proposal to exclude the 12-17 year old age group given the negative trends seen in your phase 3 program. How adolescent data will be handled will be a review issue.*

**DISCUSSION:**

There was no discussion held for this response.

***Question 4: The data from SIROCCO and CALIMA show that both a prior history of exacerbations and baseline eosinophil level are independent potential predictors of treatment benefit. It is the Sponsor's assessment that this information is clinically relevant to the prescriber in better identifying patients who are more likely have an eosinophilic phenotype and helps to inform the responder patient population to benralizumab. Does the Agency agree? If so, does the Agency agree that this information should be included in the labeling information?***

**FDA Response:**

*A prior history of exacerbations and baseline eosinophil levels as independent predictors of treatment benefit would warrant further review. How these data will be presented in product labeling will be a review issue.*

**DISCUSSION:**

There was no discussion held for this response.

**Question 5:**

- (a) *The Sponsor considers the additional analyses of exacerbations associated with hospitalizations and ER visits to be important information to include in the prescribing information to further describe benefit related to the primary endpoint of annual asthma exacerbation rate. Does the Agency agree?*
- (b) *The results of these analyses from SIROCCO and CALIMA will be presented side-by-side and pooled in the Integrated Summary of Efficacy, but only the pooled analysis will be presented in the label. Does the Agency agree with this approach?*

**FDA Response:**

*We agree that data documenting a treatment's impact on exacerbations associated with hospitalization and ER visits are clinically meaningful and warrant inclusion into product labeling. Typically, results from the individual trials are presented.*

**DISCUSSION:**

There was no discussion held for this response.

**Question 6:** *Does the Agency agree with the approach for inclusion of long-term safety data in the submission package?*

**FDA Response:**

*The placebo-controlled data from your phase 3 program provide for a sufficient safety database for review of a BLA application; however we agree that the BORA data will provide useful safety information on longer term use.*

**DISCUSSION:**

There was no discussion held for this response.

**Question 7:** *The Sponsor will include the KHK-sponsored studies in the Table of All Studies, but plans to include only the data from the AZ-sponsored studies in the clinical or safety sections of the benralizumab BLA. Does the Agency agree with this approach?*

**FDA Response:**

*Your approach is reasonable. We request that you clearly identify which studies are KHK-sponsored in your application and in the Table of All Studies.*

**DISCUSSION:**

There was no discussion held for this response.

**Question 8:** *Does the Agency agree with the proposal to evaluate bioavailability and covariate effects by the population modelling approach?*

**FDA Response:**

*In general, your proposal seems reasonable; however acceptability will be a review issue, and will be determined upon review of the actual data submitted in the BLA.*

**DISCUSSION:**

There was no discussion held for this response.

**Question 9:**

(b) (4)

**FDA Response:**

(b) (4)

**DISCUSSION:**

There was no discussion held for this response.

**Question 10: Does the Agency agree with the proposed pooling strategy for the integrated summaries?**

**FDA Response:**

*Overall, we concur with your plan to pool data from SIROCCO and CALIMA; however, data from the individual trials in addition to data from your pooling will be considered during the review process. Given the difference in treatment exposure in SIROCCO and CALIMA, the review of the pooled safety data will primarily rely on your planned exposure-adjusted analysis. In addition to your planned analyses, provide adverse event tables with pooled data of equal treatment duration from CALIMA and SIROCCO (e.g., first 48 weeks of data from CALIMA with data from SIROCCO). This latter analysis should be used in Section 6 of your proposed product labeling.*

**DISCUSSION:**

MedImmune referred to their clarification document which states:

*The Sponsor understands that the purpose of the additional analysis requested is to inform the content in Section 6 of the proposed product label. As such, in addition to the planned pooled presentations of safety data outlined in the Integrated Summary of Safety (ISS) Statistical Analysis Plan (SAP), the Sponsor intends to provide pooled summary tables of adverse events (AEs) by preferred term (PT), in decreasing order of frequency, for the on-treatment period in SIROCCO and CALIMA with the on-treatment period truncated to 48 weeks (336 days) in both studies. In addition, 2 summary tables in the same format as those for AEs will be provided to summarize serious adverse events (SAEs) and AEs leading to permanent discontinuation of investigational product (DAEs) for the same 48-week on-treatment period.*

*Please note that these summary tables will exclude any on-treatment AEs or SAEs with onset after Day 336, although these events will be included in the pre-specified analyses outlined in the ISS SAP.*

The FDA acknowledged the response and noted that the proposal is in alignment with what was requested.

***Question 11: Does the Agency agree that the proposed analyses and subgroups are acceptable?***

**FDA Response:**

*The proposed analyses and subgroups are generally reasonable, although we have the following recommendations for the proposed integrated analyses:*

- *Include in your integrated analyses a comparison between the two benralizumab 30 mg regimens, Q4W and Q4W followed by Q8W.*

**DISCUSSION:**

MedImmune referred to their clarification document and asked the FDA to clarify what data is needed. The FDA acknowledged that there are no planned analyses to compare benralizumab 30 mg Q4W versus Q4W followed by Q8W in the individual pivotal studies. The statistical analysis plan specifies that each of the two benralizumab doses will be compared to placebo for exacerbation and other endpoints. With data available and as an exploratory analysis, the FDA suggested that MedImmune make a direct comparison between the two benralizumab dose regimens, 30 mg Q4W and Q4W followed by Q8W, in order to gain better understanding about dose selection and to evaluate the risk-benefit ratio. MedImmune stated that the integrated analyses comparing the two benralizumab 30 mg regimens, Q4W and Q8W, will be post hoc and no multiplicity adjustment will be applied. The FDA stated this appears reasonable.

- *Analyze the baseline blood eosinophil count as a continuous variable in both the individual studies and the integrated efficacy analysis to further explore the potential interaction between baseline eosinophil level and the effect of benralizumab.*

**DISCUSSION:**

The FDA stated that for baseline eosinophil counts, MedImmune enrolled one-third of patients with a count of less than 300/uL and others had a count of at least 300/uL. The use of 300/uL as a threshold is somewhat arbitrary and more precision in evaluating the eosinophil-by-treatment interaction can likely be achieved by including the baseline eosinophil count as a continuous variable in the analysis. The additional requested analysis model should include a term for the continuous eosinophil count by treatment interaction.

- *For adverse events of special interest, we agree with your planned descriptive statistical analyses but also recommend additional integrated analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, or rate ratio, along with a confidence interval for the metric used*

*for comparison). These analyses should appropriately account for study differences, either by adjusting or stratifying by study. The Miettinen and Nurminen's score method you mention as a possibility would be a reasonable approach.*

**DISCUSSION:**

MedImmune referred to their clarification document and asked the FDA if their proposal for grouping events and potential risks are acceptable. The FDA stated that the proposal is generally acceptable and recommended including additional relevant adverse events, such as zoster which was included in their press release. The FDA asked MedImmune how they intend to handle the safety analysis with regards to anaphylaxis. MedImmune stated they will use Sampson criteria, which was acceptable to the FDA.

MedImmune noted that no REMS is planned to be submitted and they do not currently foresee the need for an advisory committee meeting, PMCs, or PMRs. The FDA acknowledged the statement and noted the need for each of these will be determined upon review of the application. MedImmune noted the BLA submission is targeted for the second half of November 2016.

***Question 12: The Sponsor has the following questions related to this data package.***

***(a) Does the Agency agree with the proposed plans for inclusion of study level datasets in the BLA?***

**FDA Response:**

*We agree.*

***(b) Does the Agency agree with the proposed plan for inclusion of pooled datasets in the BLA?***

**FDA Response:**

*We agree.*

***(c) Does the Agency agree that the proposed approach for handling adjudicated datasets is acceptable?***

**FDA Response:**

*Ensure that your submitted datasets include all recorded events (regardless of the adjudication outcome), as well as the result of the adjudication process.*

***(d) Does the Agency agree that the inclusion of the software programs for the creation of ADaM datasets and the tables, listings, and figures for the primary and secondary endpoints is sufficient for the Agency to recreate in their environment?***

**FDA Response:**

*We agree.*

**DISCUSSION:**

There was no discussion held for responses to Question 12.

***Question 13: Does the Agency agree that the proposed package for the OSI is acceptable?***

**FDA Response:**

*We agree with your plan to follow the Draft Guidance regarding Summary Level Information and Data requirements for CDER's Inspection Planning. However, based on advice from the tool development team, the dataset should not be altered and all sites should be included in the dataset for the tool to work properly. We acknowledge your concerns regarding the number of sites that randomized small numbers of patients; however, the tool is designed to account for this.*

**DISCUSSION:**

There was no discussion held for this response.

**Nonclinical comment:**

*A safety assessment of leachables (and extractables, as appropriate) with the accessorized prefilled syringe should be included with the BLA.*

**DISCUSSION:**

There was no discussion held for this response.

**3.0 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. 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 PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **PRESCRIBING INFORMATION**

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

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

### **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 September 19, 2016, and officially submitted to the IND on September 20, 2016.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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COLETTE C JACKSON  
10/27/2016



IND 100, 237

**MEETING MINUTES**

MedImmune  
One MedImmune Way  
Gaithersburg, Maryland 20878

Attention: Steve Danielson  
Senior Director, Global Regulatory Affairs

Dear Mr. Danielson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Benralizumab (MEDI-563).

We also refer to the meeting between representatives of your firm and the FDA on February 13, 2013. The purpose of the meeting was to discuss your clinical strategy and design for your proposed Phase 3 clinical studies. .

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

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B

**Meeting Category:** End of Phase 2

**Meeting Date and Time:** February 13, 2013, at 11 am EST

**Meeting Location:** White Oak Building 22, Conference Room 1415

**Application Number:** IND 100, 237

**Product Name:** Benralizumab (MEDI-563)

**Indication:** Asthma

**Sponsor/Applicant Name:** MedImmune

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.

**Meeting Recorder:** Colette Jackson

### FDA ATTENDEES

#### Center for Drug Evaluation and Research:

##### Office of Drug Evaluation II, Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, M.D., Ph.D., Division Director  
Sofia Chaudhry, M.D., Clinical Reviewer  
Susan Limb, M.D., Clinical Team Leader  
Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer  
Colette Jackson, Senior Regulatory Health Project Manager

##### Office of Biotechnology Products

Marjorie Shapiro, Ph.D., Product Team Leader

##### Office of Biostatistics, Office of Translational Sciences

Gregory Levin, Ph.D., Statistical Reviewer  
Joan Buenconsejo, Ph.D., Statistical Team Leader

Sue Jane Wang, Ph.D., Office Associate Director for Pharmacogenomics and Adaptive Design

Office of Clinical Pharmacology, Office of Translational Sciences

Ping Ji, Ph.D., Clinical Pharmacology Reviewer  
Suresh Doddapaneni, Ph.D., Acting Clinical Pharmacology Team Leader

Office of Surveillance and Epidemiology

Division of Medication Error Prevention and Analysis

Lubna Merchant, Team Leader  
Lissa Owens, Safety Evaluator

Division of Risk Management

Yasmin Choudhry, M.D., Safety Evaluator

Office of New Drugs

John Jenkins, M.D., Director

Office of New Drugs, Pediatric and Maternal Health Staff

Denise Pica-Branco, Senior Regulatory Health Project Manager  
Jeanean Best, MSN, RN, PNP, Senior Clinical Analyst

**Office of Special Medical Programs, Office of Combination Products:**

Patricia Love, M.D., Deputy Director

**Center for Devices and Radiological Health:**

Jacqueline Ryan, Ph.D., Scientific Reviewer, DAGID/GHDBR  
Quynh Nhu Nguyen, Human Factors Specialist, DAGRID/HFPMET

**SPONSOR ATTENDEES:**

**MedImmune**

Steven Caffè, M.D. Senior Vice President, Global Regulatory Affairs  
Ross Lobell, Vice President, Global Regulatory Affairs  
Steve Danielson, Senior Director, Global Regulatory Lead, benralizumab program  
Li Li, Ph.D., Associate Manager, Regulatory Project Management

Chris Ward, Ph.D. Principal Scientist Translational Sciences  
Scott Manetz, Ph.D., DABT, Senior Toxicologist  
Lorin Roskos, Ph.D. Vice President, Clinical Pharmacology & DMPK  
Bing Wang, Ph.D., Fellow, DMPK  
Xiao Xu, Ph.D., Director, HOPE  
Donald Raible, M.D., Senior Director, Clinical Development  
Patricia Cash, Ph.D., Senior Director, Biopharmaceutical Development  
Milton J. Axley, Ph.D., Director, CMC Team Leadership  
Andy Donnelly, Ph.D., Associate Director, Drug Delivery and Device Development  
Suzanne Kiani Associate Director, Regulatory CMC

### **AstraZeneca**

Mitch Goldman, M.D., Medical Science Director and Clinical Lead  
Tom Uryniak, M.S. Director, Statistical Science, benralizumab project statistician  
Doug Smith, Vice President, Global Product Development  
Catherine Bonuccelli, M.D., Clinical Vice President, Inflammation, Neuroscience and Respiratory, Global Medicines Development

## **1. BACKGROUND**

MedImmune sent in a meeting request dated November 9, 2012, to discuss their clinical strategy and design for their proposed Phase 3 clinical studies. The briefing package was received on January 14, 2013. Upon review of the briefing package, the Division responded to MedImmune's questions via fax on February 12, 2013. The content of that fax is printed below. 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**

### ***Questions for Chemistry, Manufacturing, and Controls (CMC)***

#### ***Question 1:***

(b) (4)  
*the intended presentation of benralizumab Drug Product for Phase 3 is a liquid formulation in a prefilled syringe (PFS), compared to the Phase 2b asthma study MI-CP220 that used (b) (4) (Process 2). These changes, along with their rationale and the comparative testing strategy, are described in Section 10. Does the Agency agree that the proposed comparative analytical testing strategy is sufficient to demonstrate comparability between Process 2 and Process 3 materials in support of the use of Process 3 material in Phase 3 studies?*

**FDA Response:**

*The methods proposed to assess comparability between Process 2 and Process 3 benralizumab drug substance and drug product are appropriate, but we have additional comments concerning the overall approach.*

*For drug substance, the comparison of three Process 2 lots with three Process 3 lots is acceptable; however we have concerns with your pre-specified acceptance criteria. It is not clear how many lots of Process 2 materials have been manufactured, but for routine release methods, the acceptance criteria should be quantitative based on the data from all previous lots. For many methods the criteria are “Report P2 results”, “Consistent with reference standard”, or “Report %”. Since capillary based methods are used for size and charge variants, you should be able to derive quantitative acceptance criteria. For cIEF, you should be able to determine an acceptable range for the main peak and a upper criteria for total acidic or basic peaks. You should justify your approach for establishing the comparability acceptance criteria.*

*We recommend providing quantitative results for the oligosaccharide peaks.*



**Question 2:** *The benralizumab Drug Substance and Drug Product specifications were revised to reflect the proposed Phase 3 formulation and presentation and are provided in Section 10. Does the Agency agree with the proposed Drug Substance and Drug Product specifications?*

**FDA Response:**

*By the time of late stage clinical development, release specifications should be quantitative. They may still be somewhat broad, but justified based on manufacturing and clinical experience. We recommend that you establish quantitative release criteria for reducing and non-reducing gel electrophoresis, and the % aggregates and fragments detected by HPSEC, % main, acidic and basic peaks for cIEF.*

***Additional Quality Comments:***

1.

2.

3.

4.

(b) (4)

5.

6.

7.

(b) (4)

***Questions for Nonclinical Studies- Pharmacology/Toxicology***

***Question 3: Does the Agency agree that the nonclinical safety program data to date, including carcinogenicity risk assessments, are sufficient to support initiation of Phase 3 studies and registration of benralizumab for the treatment of adult and adolescent patients as defined in the proposed asthma indication?***

**FDA Response:**

*We agree that the nonclinical safety program data to date, including carcinogenicity risk assessments, are sufficient to support initiation of the clinical trials described in the meeting package.*

*Subjects enrolled in clinical trials should be monitored for potential development of tumors.*

*It appears premature to discuss registration, although based upon information available at this time, it is unlikely that additional nonclinical studies would be required for the filing of a BLA.*

***Questions for Clinical Studies***

**Introductory Comments:**

*We have concerns regarding the scope and cohesiveness of the proposed development program for benralizumab. Based on our review of the briefing materials, we are unable to confirm the proposed dose and target patient population. As there is no agreed-upon definition of "eosinophilic asthma," defining an appropriate patient population that can be reliably identified in a real-world setting is critical. Furthermore, while we agree that a reduction in exacerbation claim is reasonable and clinically meaningful,*

(b) (4)

(b) (4)

*The following are high-level comments regarding the proposed program.*

1. *Studies 1, 2, and 6 evaluate patients with a peripheral eosinophil count  $\geq 300$  cells/ml* (b) (4)

*In contrast, Studies 3 and 4 do not have a requirement for eosinophilia* (b) (4)

*It is unclear which patient population you feel would most benefit from benralizumab, and the rationale for the overall plan seems somewhat self-contradictory. We recommend that you refine your target population prior to starting your confirmatory trials.*

2. *As noted above, there are no clear diagnostic criteria for eosinophilic asthma. While use of a threshold value for peripheral eosinophilia to identify patients is acceptable in principle as an enrichment strategy, the program will need to provide data to justify the proposed cut-off value. Information regarding a lack of effect in patients that do not meet the criterion will be important for labeling. In addition, the program should address the appropriate duration of treatment since eosinophilia will be suppressed on benralizumab. We question the adequacy of the data generated to date to meet these requirements.*

### **Discussion:**

MedImmune referred to introductory comments #1 and #2, noting that their trials are designed to prove the benefit of benralizumab in patients with an eosinophilic component to their asthma. MedImmune intends to use an eosinophilia cutoff of 300 cells/mcl in Studies 1, 2, 3, and 6. The FDA stated that using eosinophilia as an enrichment criterion was acceptable in principle; the intent of the introductory comment was to ensure that a clear patient population is identified, given the absence of an agreed-upon definition for eosinophilic asthma. Delineation of a distinct patient population will be required for labeling, including information on those patients who are not expected to benefit from benralizumab, i.e., patients with eosinophil counts <300 cells/mcl. FDA noted that the currently available information was not likely to be adequate for labeling purposes and recommended that MedImmune conduct further evaluation to confirm the proposed eosinophilia cutoff.

MedImmune noted that they are willing to work with other markers of asthma other than eosinophil levels and asked the FDA for advice. FDA responded that selection of a biomarker or different enrichment criterion was at MedImmune's discretion; such parameters would need to be supported by clinical data as discussed for the eosinophil cutoff.

MedImmune stated that in addition to the eosinophil cutoff, historical eosinophil values or hospitalization history may also be used as enrichment criteria. FDA cautioned that additional restrictions of the patient population may make it difficult to describe the target patient population adequately in the label.

(b) (4)  
MedImmune clarified that they intend to provide information on hospitalizations as (b) (4) supportive information, (b) (4) MedImmune asked the FDA if it is acceptable to adjudicate the hospitalization data in order to tease out the regional and socio-economic differences seen. The FDA stated that this is an acceptable approach.

FDA asked MedImmune to consider the appropriate duration of treatment. FDA asked MedImmune to address whether benralizumab is intended as life-long therapy or if it is intended for more intermittent use. MedImmune noted that they will take this into account and clarify at a later time.

- We generally expect the full spectrum of asthma severity to be assessed in an asthma development program. As previously conveyed in the written communication dated January 27, 2012, the program will need to provide justification for the restriction of use to a more severe patient population. Information regarding a lack of effect or an unfavorable risk-benefit ratio will be important for labeling.*

**Discussion:**

MedImmune noted that they defined their proposed patient population based on unmet need. Patients who are less ill are less prone to exacerbations and an expensive biologic would not be used in this patient population. MedImmune is targeting the more severe asthma patient population and believes that benralizumab will be inappropriate for patients with less severe forms of asthma. FDA requested that MedImmune provide the rationale in the application.

- The proposed indication specifies (b) (4)  
(b) (4)  
The ACQ alone is insufficient. We refer you to the "Guidelines for the Diagnosis and Management of Asthma (EPR-3)" regarding the criteria for assessment of asthma control.*

(b) (4)

**Discussion:**

MedImmune stated that the intent of their steroid sparing trial is [REDACTED] (b) (4) to demonstrate the ability to reduce the patient use of steroids and the number of exacerbations while using this product. MedImmune noted that the trial was intended to satisfy regulatory requirements in the US and abroad. FDA expressed concern with this concept for the reasons outlined in the preliminary response and clarified that such a trial was not a requirement in the US.

6. *We question the relevance* [REDACTED] (b) (4)

7. *We are unable to confirm the proposed dose of 30 mg administered every 4 weeks for 3 doses followed by dosing every 8 weeks. We recommend basing dose selection on a clinically relevant endpoint, such as exacerbations. The clinical relevance of the treatment difference observed in the available exacerbation data is somewhat uncertain. While the decision to use pharmacodynamic modeling to guide dose selection is at your discretion, we caution you that there are conflicting data in the literature regarding the relationship between eosinophilia and asthma severity. Therefore, dose selection based primarily on a biomarker of uncertain clinical relevance is risky. We recommend that you conduct further dose exploration and consider inclusion of more than one dose into your phase 3 development program.*

**Discussion:**

MedImmune clarified that the modeling conducted in support of their recommended dose of 30 mg was not based solely on the eosinophil biomarker, but on the primary and secondary efficacy endpoints, including exacerbations, FEV1, and ACQ. MedImmune stated that lower doses were not likely to be efficacious and were more likely to be associated with increased PK variability and anti-drug antibody (ADA) formation.

FDA stated that pharmacodynamic modeling to assist in dose selection was acceptable in principle. However, FDA questioned the strength of the data used in the model. The number of patients who experienced an exacerbation in the Phase 2 trials was fairly limited, so the modeling data is based on limited data points. Thus, FDA cannot confirm the dose proposed for Phase 3 trials based on the available information. FDA acknowledged the difficulty in dose-ranging for an endpoint such as asthma exacerbations; therefore, FDA recommended inclusion of more than one dose in the pivotal efficacy trials.

8. *We note the fairly high rate of anti-drug antibody (ADA) development which has been observed to date and acknowledge your plan to assess the pharmacokinetic exposure to benralizumab in your confirmatory trials. Significant decreases in systemic exposure over time or safety concerns related to the development of ADA may impact the viability of the program.*

**Discussion:**

FDA noted that the high rate of ADA formation may be problematic. While the use of higher doses to suppress ADA formation has been an acceptable strategy for other biologic products, the acceptability of this approach has relied on the specific risk-benefit assessment for other indications. In other words, a higher degree of immunosuppression and its accompanying safety risks may be acceptable for a severe and potentially disfiguring disease such as rheumatoid arthritis. Whether a similar risk-benefit ratio would be acceptable for a disease like asthma has yet to be determined. MedImmune agreed to provide analyses of ADA titers in relation to various PK parameters and adverse events in the Phase 3 program.

In addition, the FDA suggests evaluating specific anti-benralizumab IgE levels. The FDA noted that IgE has a short half-life and the assay used must be sensitive to capture the levels in the bloodstream.

***Question 4: Does the Agency agree that data generated in the ongoing studies and the proposed registration studies would represent a sufficient efficacy and safety database to support the registration of benralizumab for the proposed asthma indication (refer to Section 3)?***

**FDA Response:**

*While the proposed size of the safety database appears reasonable at this time, the adequacy of your safety database will depend on the nature of the safety data. Refer to the Introductory Comment regarding the efficacy database.*

**Discussion:**

MedImmune asked the FDA to confirm that the 48-week treatment duration of their primary registration trials is acceptable. The FDA stated that this duration appears reasonable.

***Question 5: The Sponsor proposes the use of hematology analyzers approved for clinical use by local regulatory authorities to quantify blood eosinophil counts in whole blood according to the assay specifications for the instrument for the purpose of enrolling subjects in the Phase 3 studies. Does the Agency agree?***

**FDA Response:**

*Yes, the proposal is reasonable.*

***Question 6: The Sponsor proposes to enroll in the Phase 3 studies only those subjects whose blood eosinophil counts are equal to or above the predefined 300 cells/ $\mu$ L cutpoint based on data generated from the Phase 2b asthma study MI-CP220 and are accordingly identified as "eosinophilic" (see Section 12.5.1.1). Does the***

***Agency agree with the blood eosinophil count cutpoint and the Phase 3 study approach?***

**FDA Response:**

*No, we can not agree at this time. Use of a peripheral eosinophil cutoff in your phase 3 trials is at your discretion, but we can not confirm your selected cutoff based on the limited data available. Refer to our Introductory Comments.*

**Question 7: The Sponsor proposes** [REDACTED] (b) (4)

***Does the Agency agree that this is appropriate?***

**FDA Response:**

*No, we do not agree.* [REDACTED] (b) (4)

*As noted in the written communication dated January 27, 2012, we expect the clinical program to evaluate the full spectrum of asthma disease severity or provide data to justify focusing on a subset of the disease. Refer to our Introductory Comments.*

**Question 8: Does the Agency agree with this definition of an asthma exacerbation, and the methodology for capturing these data in the Phase 3 studies?**

**FDA Response:**

*Yes, the proposed definition is reasonable.*

**Question 9: The sponsor considered all available safety and efficacy data, as well as population exposure-response modeling, and stochastic trial simulations in selecting the proposed dose of 30 mg and dosing regimen (every 4 weeks [Q4W] for the first 3 doses and every 8 weeks [Q8W] thereafter) for the Phase 3 benralizumab program. Does the Agency agree with our choice of dose selection and regimen?**

**FDA Response:**

*No, we can not agree at this time. We acknowledge the rationale for the choice of dose selection and regimen to be carried into phase 3 program. However, information presented in the meeting package was not extensive enough to fully understand the technical details of the exposure response modeling. Further, it is not clear that you have fully explored the dose response to identify the optimal dose(s) to be carried into the Phase 3 program that will provide the best*

*risk/benefit profile. It is not known at this time if doses between 2 mg and 20 mg are viable.. We suggest that you consider exploring doses lower than 20 mg. However, you may proceed at your own risk. Refer to our Introductory Comments.*

**Question 10:** *The preclinical literature on the role of eosinophils in host defense against helminthic parasites is conflicting. One report in the literature showed that ablation of eosinophils with anti-IL-5 antibody in mice enhanced the survival of *Trichinella spiralis* (Vallance et al, 2000). On the other hand, depletion of eosinophils in other murine *T spiralis* infection models have shown no effect (Herndon and Kayes, 1992) or even a detrimental effect (Fabre et al, 2009) on the ability to clear parasitic infections. For Phase 3, we plan only to exclude those subjects who have not been shown to have been successfully treated for a recent helminthic parasite infection. We will not employ stool parasite screening. However, in endemic countries, we will adhere to evaluation for suspected helminthic parasite infections according to the local standard of care as determined by local guidelines (including stool for ova and parasites), if indicated/necessary. Does the Agency agree with this approach?*

**FDA Response:**

*This approach appears reasonable from a safety perspective. However, we remind you that failure to properly exclude other causes of elevated eosinophil counts in patients has the potential to negatively impact your ability to detect a treatment effect. In addition, we note that the same peripheral eosinophil cutoff may not be relevant across all study sites (i.e., in endemic areas versus non-endemic areas).*

**9.4 Safety and Immunogenicity Assessments**

**Question 11:** *As discussed in the FDA Safety and Innovation Act of 2012 (FDASIA) guidance, the Sponsor is considering inclusion of a benefit-risk assessment structured in [REDACTED] (b) (4) or similar format in the BLA for this program. Would that format be useful to the Agency in assessing the merits of our data at the time of submission? Does the Agency have an alternate preference for format at this time?*

**FDA Response:**

*Given the current stage of development, discussion of the format for the NDA's benefit-risk assessment appears premature.*

**Question 12:** *The Sponsor proposes an immunogenicity analysis strategy during Phase 3 that provides anti-drug antibody (ADA) assessments using a tiered approach (screen, confirm, titer) with a drug-tolerant electrochemiluminescent (ECL)-*

*based immunoassay, at steady state trough concentrations and for additional testing periods after cessation of therapy. During assay validation, the benralizumab ADA screening assay was shown to detect 25 ng/mL and 100 ng/mL of ADA in the presence of 10 µg/mL of drug as assessed by surrogate polyclonal and monoclonal ADA controls, respectively. The 10 µg/mL drug tolerance greatly exceeds the projected steady-state trough concentration of benralizumab at the highest dose level investigated (100 mg) in the Phase 2 asthma Study MI-CP220. The proposed Phase 3 dose of 30 mg is lower than the highest dose studied in Study MI-CP220 (100 mg).*

*Anti-drug antibody measurements in Phase 3 will be assessed in association with safety, efficacy, and pharmacodynamics (PD, blood eosinophil counts). Analyses will be conducted to compare the pharmacokinetic (PK)/PD profiles of ADA-positive and ADA-negative subjects.*

*Neutralizing antibody (nAb) assessments in Phase 3 will be assessed with a competitive ligand binding assay following extensive investigation of the interrelationship of PK, PD (blood eosinophil depletion and recovery), ADA titers by ECL immunoassay, and nAb with the Phase 2b blood samples from asthma subjects in Study MI-CP220. The samples from asthma subjects in Study MI-CP220 will be tested for nAb both by competitive ligand binding assay (potential of nAb to inhibit the interaction of benralizumab with recombinant soluble interleukin-5 receptor [IL-5R]), and if successively validated, by bioassay. It is the Sponsor's assessment that, due to matrix (serum from the patient samples) and drug tolerance issues, the bioassay is likely to be poorly sensitive in its ability to detect nAb. In contrast, the blood eosinophil count measurement as a direct readout of benralizumab in vivo activity will be a more effective assessment of any true biological impact of nAb. Therefore, our approach on nAb will be an integrated assessment of the PK/PD (eosinophil count) relationship, the ADA titer, and the competitive ligand binding nAb results.*

*Does the Agency consider the plan proposed above adequate for assessing anti-drug antibody (ADA) responses to benralizumab (Section 12.4)?*

**FDA Response:**

*The proposed analysis plan appears reasonable for assessing ADA responses during phase 3 clinical trials.*

**9.5 Other**

**Question 13:** *As there is no evidence that eosinophils are involved in drug metabolism or that interleukin-5 (IL-5) has any impact on common drug metabolism pathways, the*

***Sponsor is not planning to conduct any drug-drug interaction studies with benralizumab. Does the Agency agree?***

**FDA Response:**

*Based on the current state of knowledge for therapeutic proteins, we agree that drug-drug interaction studies are not needed at this time.*

***Question 14: The Sponsor plans to include adults and adolescents (12-17 years of age) in the pivotal Phase 3 studies. While patients 12 - 17 years of age have not previously been studied in the benralizumab program, it is the Sponsor's assessment that pharmacokinetic (PK) modeling and safety data from the adults studied support inclusion of adolescents down to 35 kg in Phase 3 studies. We will request a deferral for studies in children (b) (4)-11, and a waiver for children (b) (4) years of age. Details of the proposed pediatric program will be provided to the Agency within 60 days of this EOP2 meeting. Does the Agency agree?***

**FDA Response:**

*Your Pediatric Study Plan (PSP) must be reviewed and agreed upon by the Pediatric Review Committee (PeRC) prior to initiating studies in the pediatric population; however, there should be sufficient evidence of effectiveness for Benralizumab in adult patients with asthma as well as sufficient short and long-term safety data in adult patients to support the initiation of pediatric trials with this product for asthma. We note that there are limited efficacy and safety data at this time to support the inclusion of patients 12-17 years of age in the benralizumab program. Please submit your Pediatric Study Plan (PSP) for review within 60 days of your EOP2 Meeting as required by the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Your PSP must include the following:*

- 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, along with supporting information. (Note: Although requests must be submitted with PSP, decisions on whether or not waivers and deferrals will be granted do not become final until approval.)*

*A copy of the Pediatric Study Template is attached.*

**Discussion:**

*MedImmune asked the FDA for feedback on their proposal to include pediatric subjects ages 12-17 years in their Phase 3 program based on the modeling data. The FDA stated that the PSP must be submitted within 60 days of this EOP2 meeting. The PSP will be discussed by the*

Pediatric Review Committee (PeRC) and FDA will provide written comments or discuss the PeRC recommendations with MedImmune within 90 days of submission. The FDA emphasized that, for this monoclonal antibody, efficacy and safety must first be established in the adult patient population prior to administering in the pediatric population.

**POST-MEETING COMMENT:**

A template is available to aid sponsors in formulating a Pediatric Study Plan:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf>

***9.6 Statistical***

***Question 15: We plan to analyze the exacerbation rate data using a negative binomial model with covariates of treatment group, country/region, number of exacerbations in the year before the study, and possibly ICS dose category (medium or high) and the use of maintenance oral corticosteroids. Does the Agency agree with this approach?***

**FDA Response:**

*This approach is reasonable. You should clearly indicate in the Phase 3 protocols the covariates that will be included in the model. We also note that estimates of the treatment effect on exacerbation rate may be biased in the presence of missing data. In order to limit missing data, we recommend that you continue to perform all scheduled safety and efficacy assessments through the complete follow-up period on patients who stop taking the treatment (placebo or benralizumab).*

***Question 16: Multiplicity methods will depend on the study design and identification of key secondary variables. Methods may include a simple step-down procedure through pre-identified secondary variables and the application of the Hommel (Hommel, 1989) procedure for secondary variables provided the difference for the primary variable is statistically significant. Does the Agency agree with this approach?***

**FDA Response:**

*The use of a simple step-down procedure through pre-specified secondary variables is reasonable. However, the method should provide strong control of the type I error without any assumptions about the joint distribution of the p-values for testing the various secondary endpoints.*

**Question 17:** *Because the exacerbation rate and scale (nuisance) parameter from the negative binomial model can have a large impact on the sample size necessary to achieve a stated power (90% in our case), we plan to conduct a blinded estimate of the placebo exacerbation rate and scale parameter at one point (yet to be determined) in each study in which the rate of exacerbations is an outcome measure. This may be used to re-estimate sample size for a given study. Is this acceptable to the Agency?*

**FDA Response:**

*The use of a blinded interim analysis to re-estimate the sample size is reasonable if it is based only on pooled data that include no information about treatment assignment. For example, a negative binomial model can be fit to the pooled, blinded data in order to use estimates of the pooled exacerbation rate and scale parameter to update the sample size.<sup>1</sup> You should describe the method and how it will be used, including pre-specification of the timing for re-estimation, in detail, and indicate how blinding will be maintained, in the phase 3 protocols.*

<sup>1</sup> Friede, T., & Schmidli, H. (January 01, 2010). Blinded sample size reestimation with negative binomial counts in superiority and non-inferiority trials. *Methods of Information in Medicine*, 49, 6, 618-24.

**9.7 Target Product Profile Claims**

**Question 18:**



**FDA Response:**

*No, we do not agree. See our introductory comments.*

**Question 19:** *In Studies 1 and 2, evidence of asthma will be documented* (b) (4)

[Redacted]

*. Does the Agency agree that these criteria are sufficient and that it is acceptabl* (b) (4)

**FDA Response:**

*No, we do not agree with the* (b) (4)

**Question 20:** *Study 3 is designed to demonstrate that subjects in the enrolled population can successfully reduce their oral prednisone usage by at least 50% and still maintain appropriate control of their asthma symptoms.* (b) (4)

[Redacted]

**FDA Response:**

*No, we do not agree. See our introductory comments.*

**Question 21:** (b) (4)

[Redacted]

(b) (4)

**FDA Response:**

*No, we do not agree. See our introductory comments.*

**Question 22:**

(b) (4)

**FDA Response:**

*No, we do not agree. See our introductory comments.*

**Question 23:** *In the proposed Phase 3 studies of benralizumab, the Sponsor will also evaluate several secondary endpoints. Does the Agency agree that sequence and method of statistical analyses of these secondary endpoints are appropriate for supporting the respective individual claims in the proposed Target Product Profile (TPP)?*

**FDA Response:**

*See response to Question 16 and our introductory comments.*

**9.8 Patient Reported Outcomes**

**Question 24:** *The FDA response letter to our request for comment on the ASMA diary dated 12May2012 stated that:*

*“the Division remains comfortable with the current approach used in labeling for asthma products that compares mean change in scores in a 3-point “symptom score” (see asthma product labels, eg, Symbicort)”*

*We reviewed the product labels and symptom measures of the approved asthma products and note that all the approved products used the single item to capture data on patient-reported asthma symptoms. This approach is consistent with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines that indicate, given the heterogeneous nature of the asthma patient population, an assessment of asthma symptoms as single concept is preferable to the assessment of individual symptoms. However, in the second paragraph of the response letter, the Agency commented:*

 (b) (4)

*In order to be consistent with the Agency’s preference for a symptom score similar to that which was used for Symbicort® (budesonide/formoterol) and the clinical guidelines, we propose to retain the overall asthma symptom questions in our current diary.*

*Does the Agency agree that a single item is sufficient for capturing asthma symptoms?*

**FDA Response:**

*As discussed in the Division comments dated May 12, 2012, the assessment of asthma symptoms as was done in previous asthma development programs is generally acceptable.*  (b) (4)

**Question 25:** *To address the stated concern about the patient instructions embedded in Item 1, we propose to*  (b) (4) *modify the overall ASMA diary instructions from:*

 (b) (4)

*To the following:*

*Please complete ALL questions by selecting the response that best describes your asthma. Asthma symptoms may include, but are not limited to, shortness of breath, wheezing, coughing, and/or chest tightness.*

***Does the Agency agree that this change addresses the stated concern?***

**FDA Response:**

*This change appears reasonable.*

***Question 26: We note that the Agency previously accepted daily diary data collected in the Symbicort studies to support asthma symptom improvement claims. For our Phase 3 studies we propose using a daily diary similar to that used in the Symbicort studies but with modifications based upon the evidence obtained from our qualitative studies of our biologic-eligible patient population (see Section 12). The Assessing Symptoms of Moderate-to-Severe Asthma (ASMA) diary will measure the same concepts as the Symbicort diary including daytime symptom severity, nighttime symptom severity, rescue medication use, and nighttime awakening but will do so with a 5-point Likert-type scale as opposed to the 4-point scale used in the Symbicort diary. Further, based on qualitative evidence obtained from patients in our target population, we have included an item to capture data concerning symptom frequency.***

***Does the Agency agree that the content of the ASMA diary is suitable for collecting symptom data in our Phase 3 clinical studies to support a label claim for asthma symptom improvement?***

**FDA Response:**

*The content in your ASMA diary appears reasonable;*

(b) (4)

## **9.9 Questions for Multidisciplinary Functions**

### **9.9.1 Drug Delivery Device**

***Question 27: The Sponsor has conducted a comprehensive risk assessment per ISO 14971 and applied Human Factors Engineering (HFE)/Usability analysis per ISO 62366 and in accordance with the Draft Guidance for Industry (Applying Human Factors and Usability Engineering to Optimize Medical Device Design, issued 22Jun2011). Information to support the use of the accessorized prefilled syringe (APFS) [REDACTED] for Healthcare Practitioner, [REDACTED]***

(b) (4) *in a clinical environment* (b) (4)  
*is summarized in Section 13.1.6.2.*

*Does the Agency agree that the HFE Program approach allows appropriate assessment of the use of the APFS (b) (4) to support the indicated user populations in the indicated use environments?*

**FDA Response:**

*No we do not agree. Based on your meeting package, the timelines for development of the APFS (b) (4) are unclear in your meeting package; we are unable to ascertain whether (b) (4) will be incorporated into your phase 3 trials. Based on page 241 of the briefing package it appears that you intend to develop the commercial combination product after phase 3. Your final finished (commercial) combination product(s) should be studied in your pivotal phase 3 trials. Generally we do not expect changes in the product after phase 3. As such the human factors and any iterative modifications in labeling should be complete before beginning these studies.*

*In addition to bench testing and human factors testing, the development program should include an assessment of device robustness and performance with real-life, clinical use. Therefore, we recommend that you incorporate assessment of device robustness in the proposed settings of use, i.e., healthcare setting (b) (4) into the confirmatory trials.*

*Based on available information your HFE Plan appears appropriate. However, submit a detailed summative/validation protocol along with a comprehensive use-related risk analysis for review and comment prior to implementation. In addition, provide summary results of all your formative testing, the modifications that were made, and discuss how these studies inform product design and labeling as well as the design of your final human factors summative/validation testing. Ensure that your summative/validation testing is performed on the final finished combination product along with its (b) (4) labeling and other training materials as appropriate.*

**Discussion:**

MedImmune noted that the accessorized pre-filled syringe device samples sent to the FDA in preparation for this meeting are the exact devices to be used in their Phase 3 trials. MedImmune stated that minor changes will be made to the accessorized pre-filled syringe for ergonomic and cosmetic reasons. MedImmune noted that a number of studies have been conducted on the accessorized pre-filled syringe to support its use. The FDA re-emphasized the importance of using the to-be-marketed product in their Phase 3 trials. It's a development risk if subsequent changes are made. If MedImmune makes such changes then before submitting the BLA, MedImmune should notify the FDA of any changes to the device configuration after completion of the phase 3 trials

The FDA asked MedImmune to clarify which presentations are to be used in clinical trials.

(b) (4) The pre-filled syringe formulation will be used in the pivotal trials and will be the basis of the initial BLA submission.

(b) (4)

**Question 28:**

(b) (4)

**FDA Response:**

Preliminarily we recommend that you (b) (4)  
utilize the Patient Instructions for Use in both populations. (b) (4)

(b) (4)

**Question 29:** *As detailed in Section 13.1.1.4 and Section 13.1.2.4, any minor changes to the APFS (b) (4) for the commercial presentation will be included in the license application. These changes are likely to be cosmetic and ergonomically driven and are not expected to impact Drug Product contact parts nor device functionality. These changes will be assessed for impact to form, fit, and function and appropriate qualification of the change will be demonstrated through application of risk management tools and repeated design verification and design validation (Simulated Use) testing as required. This information will be summarized in the license application.*

***Does the Agency agree that the proposed APFS (b) (4) are appropriate for the intended use and that the proposed strategy for testing to demonstrate device comparability of the Phase 3 APFS and Commercial APFS (b) (4) is acceptable?***

**FDA Response:**

*No we do not agree. Although generally the preliminary testing strategy you have proposed to demonstrate safety and efficacy of the device constituent part appears reasonable, the briefing document does not provide enough information to determine if the APFS (b) (4) and iterative changes would affect the safety and effectiveness of the combination products for their intended use. In some instances “cosmetic and ergonomic” changes could affect the performance of the final finished combination. For additional information on the comparability of the Phase 3 APFS and the commercial APFS (b) (4) see the response to question 27.*

**Question 30:**

(b) (4)

**FDA Response:**

*See the response to question 27 and our introductory comments.*

***Question 31: Administration of benralizumab (b) (4) physician’s office is a desirable goal for the development of the commercial product.***

(b) (4)

**FDA Response:**

*The label instructions for administration generally reflect the manner of administration studied in the clinical trials. (b) (4)  
See the response to question 27.*

### **3.0 OTHER IMPORTANT MEETING INFORMATION**

#### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

### **5.0 ACTION ITEMS**

There were no action items identified during the meeting

### **6.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting.

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/s/  
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COLETTE C JACKSON  
03/14/2013

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 761070

**LATE-CYCLE MEETING MINUTES**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
Wilmington, Delaware 19803

Attention: Les Thomas  
Director, Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab 30 mg/mL injection solution.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 9, 2017.

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

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Lydia Gilbert-McClain  
Deputy Division Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure: Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** August 9, 2017, at 1 PM EST  
**Meeting Location:** WO22, Conference Room 1419

**Application Number:** BLA 761070  
**Product Name:** Benralizumab  
**Indication:** Asthma  
**Applicant Name:** AstraZeneca AB

**Meeting Chair:** Lydia Gilbert-McClain  
**Meeting Recorder:** Colette Jackson

**FDA ATTENDEES**

**Office of Drug Evaluation II**

Curtis Rosebraugh, M.D., Director

**Division of Pulmonary, Allergy, and Rheumatology Products**

Badrul A. Chowdhury, M.D., Ph.D., Director  
Lydia Gilbert-McClain, M.D., Deputy Division Director  
Sofia Chaudhry, M.D., Clinical Reviewer  
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader  
Carol Galvis, Ph.D., Pharmacology/Toxicology Team Leader  
Colette Jackson, Senior Regulatory Health Project Manager

**Office of Pharmaceutical Quality, Office of Biological Products**

Sarah Kennett, Ph.D., Application Technical Lead  
Jennifer Swisher, Ph.D., Product Quality Reviewer

**Office of Pharmaceutical Quality, Office of Process and Facilities**

Maria (Reyes) Candauchaon, Ph.D., Microbiology Reviewer  
Maria Jose Lopez-Barragan, Ph.D., Microbiology Reviewer

**Office of Clinical Pharmacology**

Sury Sista, Ph.D., Clinical Pharmacology Reviewer  
Yunzhao Ren, Ph.D., Acting Clinical Pharmacology Team Leader

**Office of Biostatistics**

Yu (Jade) Wang, Ph.D., Statistical Reviewer  
Yongman Kim, Ph.D., Acting Statistical Team Leader

## **ASTRAZENECA ATTENDEES**

Colin Reisner, M.D., Head - Respiratory Global Medicines Development  
Mark White, M.D., Global Medicine Leader  
Mitch Goldman, M.D., Ph.D., VP Respiratory Biologics  
Ubaldo Martin, M.D., Global Clinical Leader  
Peter Barker, Ph.D., Global Product Statistician  
Serahe Fitzpatrick, M.D., Global Safety Physician, Patient Safety  
Milt Axley, Ph.D., Global CMC Team Leader  
Lorin Roskos, Ph.D., VP, Clin Pharm, Pharmacometrics & DMPK  
Paul Newbold, Ph.D., Fellow, Translational Medicine  
Nicole Barnor, Pharm.D., Global Labelling Lead  
Fadi Hakki, Regulatory CMC Lead  
Les Thomas, Global Regulatory Lead  
Azin Shahzamani, VP, Regulatory Affairs

### **1.0 BACKGROUND**

BLA 761070 was submitted on November 16, 2016, for Benralizumab.

Proposed indication: Asthma

PDUFA goal date: November 16, 2017

FDA issued a Background Package in preparation for this meeting on July 28, 2017.

### **2.0 DISCUSSION**

#### **1. *Introductory Comments – 10 minutes (RPM/CDTL)***

*Welcome, Introductions, Ground rules, Objectives of the meeting*

#### **2. *Discussion of Substantive Review Issues – 15 minutes***

*Each issue will be introduced by FDA and followed by a discussion.*

##### CMC

*The application references Drug Master File (DMF) (b) (4) This DMF is currently under review. Deficiencies were identified, and a deficiency letter was sent to the DMF holder; the response is currently pending.*

##### **Discussion:**

With respect to the DMF deficiencies noted in the late cycle meeting background package, the FDA stated that additional information has been received and the DMF is currently considered to be adequate.

The FDA acknowledged receipt of AstraZeneca AB's (AZ) August 4, 2017, response to the July 13, 2017, CMC information request and noted that although a thorough review has yet been

conducted, there appeared to be some remaining issues and questions for the company. The FDA stated that a formal information request will be provided on or before August 18, 2017, but wanted to briefly discuss AZ's responses to FDA comment number 1, 3, 4, 14, 21, and 22b.

In regard to AZ's response to comments #14 and #21, the FDA stated that the responses are still being considered. (b) (4)

In regard to AZ's response to comment #22b, the FDA stated it is not acceptable to extend the DP expiry period using extrapolated stability results; for example, (b) (4) months of data are required to extend the expiry period to (b) (4) months.

In regard to AZ's response to comment #1, the FDA asked whether all of the side by side testing of the PFS and APFS lots presented in the response had been conducted recently. AZ stated the data were generated within the last 2 weeks.

In regard to AZ's response to comment #3, the FDA acknowledged the proposal to change the visible particle acceptance criteria for drug substance (DS), (b) (4) and drug product (DP) from < Particle Standard (b) (4) to < Particle Standard (b) (4). Despite the proposed change in the specification, the FDA is concerned because no particles were ever detected in DP lot release testing and were only seen at isolated stability timepoints. Therefore a specification of < Particle Standard (b) (4) is unacceptable, because it would allow more than (b) (4) particles per mL. Particles were seen in the (b) (4) DS during stability studies but only at random intermediate time points; in nearly all of these cases, no particles were detected in the previous and subsequent timepoints, leaving open the possibility that the results may have been the result of improper sampling, sample handling (i.e., thawing), or operator error. In addition, AZ did not provide any characterization data regarding the nature of these particles. The FDA noted that the labeling will need to be modified to clarify that (b) (4) the syringe "(b) (4) a few particles would be acceptable. AZ stated they will discuss this internally and will respond to the FDA.

**3. Additional Applicant Data – 10 minutes (Applicant)**

**4. Information Requests – 5 minutes**

*July 13, 2017, CMC information request.*

**5. Major labeling issues – 15 minutes**

*FDA Proposed labeling comments sent July 20, 2017. Response due by July 28, 2017.*

**Discussion:**

The FDA noted that labeling negotiations are ongoing and the FDA anticipates issuing a second labeling correspondence to AZ within the next week. The FDA asked AZ for a rationale for their proposed age range of 18 years and older when the program enrolled down to 12 years of age and included a reasonable number of subjects in 12 to 17 year age range. AZ stated that it took a conservative approach requesting an indication in adults 18 years of age and older as the data did

not show efficacy signals in the adolescent population. However, AZ noted that no safety signals were seen in the adolescent population. The FDA asked if AZ saw any biological plausibility as to why the drug wouldn't work or would work differently in the 12 to 17 year old population. The FDA also asked AZ to outline their plans for the 12 to 17 year old population. AZ stated there is no biologic plausibility that it should not work in the 12 to 17 year old range for asthma as the PD effect seen was as anticipated and behaved the same as in adults. AZ also stated they have not yet looked at a path forward and currently did not have any plans outlined for further development in pediatrics.

The FDA noted that no safety issues identified with adolescent subjects, and there is no biological plausibility that the drug will not work in that age range, that the adolescent efficacy data was obtained from trials powered to demonstrate a treatment effect in the entire enrolled population and not specifically the adolescent population, and that sufficiently powered pediatric studies may not be feasible to conduct. Thus, it recommends that AZ consider submitting a proposal with justification to extend the age range for approval in asthma down to 12 years of age. AZ asked the FDA if approval in the 12 to 17 year old range reflects the input and recommendation from the Pediatric Review Committee (PeRC). The FDA stated that the application had been discussed at PeRC, but that the Agency is only requesting that AZ consider providing justification for approval down to the age of 12 years at this time. AZ stated they will discuss internally and provide a response to FDA.

**6. Review Plans – 5 minutes**

*Reviews are ongoing and on target with PDUFA goals.*

**Discussion:**

AZ asked the FDA if there is a possibility for an early action, prior to the November 16, 2017, PDUFA goal date. The FDA stated there were no plans for an early action.

**7. Wrap-up and Action Items – 10 minutes**

- *No further action items*
- *Additional questions from the Sponsor*

**Discussion:**

The FDA noted that the FDA action items forthcoming are a CMC IR in response to the August 4, 2017, submission and FDA proposed labeling. Both are anticipated to be sent to AZ by or before August 18, 2017. AZ action items are to consider submission of a justification for approval in the 12 to 17 year old age. AZ stated they will submit their justification by August 18, 2017, or sooner.

AZ asked if a license number has been generated for the application and, if so, can the number be provided in advance of action. The FDA noted that the license number is listed in the approval action letter. (**POST-MEETING NOTE:** AZ was contacted via phone shortly after the

teleconference to provide the pending license number in the BLA submission database. The FDA emphasized that this number is pending and is granted upon approval of the BLA)

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/  
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LYDIA I GILBERT MCCLAIN  
09/08/2017



BLA 761070

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

AstraZeneca AB  
c/o AstraZeneca Pharmaceuticals LP  
1800 Concord Pike  
Wilmington, Delaware 19803

Attention: Les Thomas  
Director, Regulatory Affairs

Dear Mr. Thomas:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2016, submitted under section 351(a) of the Public Health Service Act for Benralizumab 30 mg/mL injection solution.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 9, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at [Colette.Jackson@FDA.HHS.GOV](mailto:Colette.Jackson@FDA.HHS.GOV), at least one week prior to the meeting.

For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least one week prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE: Late-Cycle Meeting Background Package

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## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** August 9, 2017, at 1 PM EST  
**Meeting Location:** WO22, Conference Room 1419

**Application Number:** BLA 761070  
**Product Name:** Benralizumab  
**Indication:** Asthma  
**Applicant Name:** AstraZeneca AB

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### 1. Discipline Review Letters

No Discipline Review letters have been issued to date.

#### 2. Substantive Review Issues

The following substantive review issues have been identified to date:

##### CMC:

The application references Drug Master File (DMF) (b) (4). This DMF is currently under review. Deficiencies were identified, and a deficiency letter was sent to the DMF holder; the response is currently pending.

## **ADVISORY COMMITTEE MEETING**

An Advisory Committee meeting is not planned.

## **REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

## **LCM AGENDA**

### **1. Introductory Comments – 10 minutes (RPM/CDTL)**

Welcome, Introductions, Ground rules, Objectives of the meeting

### **2. Discussion of Substantive Review Issues – 15 minutes**

Each issue will be introduced by FDA and followed by a discussion.

#### CMC

The application references Drug Master File (DMF) (b) (4). This DMF is currently under review. Deficiencies were identified, and a deficiency letter was sent to the DMF holder; the response is currently pending.

### **3. Additional Applicant Data – 10 minutes (Applicant)**

### **4. Information Requests – 5 minutes**

July 13, 2017, CMC information request.

### **5. Major labeling issues – 15 minutes**

FDA Proposed labeling comments sent July 20, 2017. Response due by July 28, 2017.

### **6. Review Plans – 5 minutes**

Reviews are ongoing and on target with PDUFA goals.

### **7. Wrap-up and Action Items – 10 minutes**

- No further action items
- Additional questions from the Sponsor



# OSO | Office of Security Operations

## FOREIGN VISITORS DATA REQUEST FORM

|  |   |                               |             |
|--|---|-------------------------------|-------------|
| VISITOR'S FULL NAME  | <b>First</b>                                    | <b>Middle</b>                 | <b>Last</b> |
|  |   |                               |             |
| GENDER   |   | DATE OF BIRTH<br>(MM/DD/YYYY) |             |
| COUNTRY OF ORIGIN /<br>CITIZENSHIP                         |   |                               |             |
| PLACE OF BIRTH<br>(CITY AND COUNTRY)                       |   |                               |             |
| PASSPORT NUMBER  |   |                               |             |
| ISSUING COUNTRY  |   |                               |             |
| ISSUANCE DATE  |   |                               |             |
| EXPIRATION DATE<br>(MM/DD/YYYY)                            |   |                               |             |
| VISITOR'S<br>ORGANIZATION/EMPLOYER                         |   |                               |             |
| MEETING START<br>(DATE/TIME)                               | August 9, 2017, at 1PM                          |                               |             |
| MEETING ENDING<br>(DATE/TIME)                              | August 9, 2017, at 2:30 PM                      |                               |             |
| PURPOSE OF MEETING   | Industry Meeting                                |                               |             |
| BUILDING(S) & ROOM<br>NUMBER(S) TO BE VISITED              | WO22 Conference 1419                            |                               |             |
| BUILDING ENTRANCE  | WO22  |                               |             |
| FDA LABORATORIES T O<br>BE VISITED                         | None  |                               |             |
| HOSTING FDA CENTER   | CDER  |                               |             |
| HOSTING OFFICIAL   | Name: Colette Jackson                           |                               |             |
|  | Title: Senior Regulatory Health Project Manager |                               |             |
|  | Office/Bldg.: WO22 Room 3322                    |                               |             |
|  | Email: Colette.Jackson@fda.hhs.gov              | Phone: 301-796-1230           |             |
| ESCORT INFORMATION<br>(If different from Hosting Official) | Name:   |                               |             |
|  | Title:  |                               |             |
|  | Office/Bldg.:                                   |                               |             |
|  | Email:  | Phone:                        |             |

**Important:** Forms must be typed. Handwritten forms will be returned.

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/s/  
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BADRUL A CHOWDHURY  
07/28/2017