CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761033Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

NDA/BLA#: 761033 | Supplement Number: _____ | NDA Supplement Type (e.g. SE5): _____

Division Name:DPARP | PDUFA Goal Date: March 30, 2016 | Stamp Date: 3/30/3015

Proprietary Name: Cinqair

Established/Generic Name: reslizumab

Dosage Form: IV

Applicant/Sponsor: Teva Pharmaceuticals

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):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: To reduce exacerbations, relieve symptoms, and improve lung function in adults 18 years of age and older with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

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#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief 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
☒	Neonate	0 wk. 0 mo.	0 wk. 23 mo.	☒	☐	☒	☐
☒	Other	2 yr. __ mo.	11 yr. __ mo.	☒	☐	☒	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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: Studies in a small number of adolescents did not demonstrate efficacy and did raise safety concerns; additional study in adolescents would be needed prior to initating investigations in younger patients.

† 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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	12 yr. __ mo.	17 yr. __ mo.	Yes ☒	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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

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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: To reduce exacerbations, relieve symptoms, and improve lung function in children zero to less than 18 years of age with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

Q1: Does this indication have orphan designation?

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

Q2: 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#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief 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 Section 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 some or all 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
☒	Neonate	0 wk. 0 mo.	0 wk. 23 mo.	☐	☒	☐	☐
☒	Other	2 yr. __ mo.	11 yr. __ mo.	☐	☒	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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: _____

† 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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	12 yr. __ mo.	17 yr. __ mo.	Yes ☒	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

COLETTE C JACKSON
01/27/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 761033	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Cinqair Established/Proper Name: reslizumab Dosage Form: intravenous		Applicant: Teva Respiratory , LLC Agent for Applicant (if applicable):
RPM: Colette Jackson		Division: DPARP

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☒ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is March 30, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received- N/A
❖ Application Characteristics [3]	

[1] 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.
[2] 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).
[3] 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.

Reference ID: 3906479

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

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date: March 22, 2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	June 25, 2015 June 23, 2015
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None August 14, 2015 DMEPA: ☐ None October 27, 2015 DMPP/PLT (DRISK): ☐ None February 24, and 29, 2016 OPDP: ☐ None March 1, 2016 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None February 24, 2016 Other: ☐ None DPMH January 4, 2016
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	August 14, 2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC February 10, 2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(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)*	April 1, 15, and 28, May 11, June 11, July 13, August 5, 20, and 23, September 3, 23 and 24, October 8, and 29, November 16, 18, and 25, and December 2, 3, 11, 17, and 18, and 24, 2015, and January 12, and 22, February 5, 10, 18, and, 26 and March 10, 17, and 18, 2016
❖ 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	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg January 15, 2015
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg August 18, 2010
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A September 8, 2015
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A November 23, 2015
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	December 9, 2015
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None March 22, 2016
Division Director Summary Review *(indicate date for each review)*	☐ None March 2, 2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None December 30, 2015
PMR/PMC Development Templates *(indicate total number)*	☐ None March 22, 2016
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	May 29, and December 17, 2015, and March 14, 2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	December 17, 2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested October 16, 2015
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None May 29, 2015, and January 15, 2016

[5] 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).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None May 20, and December 17, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review March 18, 2016
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review December 23, 2015
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None May 19, December 16, 2015, and February 19, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc June 17, 2015
❖ ECAC/CAC report/memo of meeting	☐ None June 19, 2015 P/T review: June 30, 2015
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None December 14, 16,(2), 18 (2), and 23, 2015, February 11 (2), 23 (2), and February 29, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None December 17, 2015, and February 9, 2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	February 23, 2016
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] 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: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

COLETTE C JACKSON
03/23/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

GENERAL ADVICE

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:
Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

Please also refer to your e-mail to Commander Shiber dated February 11, 2016 in which you disclosed that the (b) (4) .

Please also refer to an e-mail to Commander Shiber dated February 29, 2016 in which you state (b) (4)

FDA recommends that you manage the release of these lots through your Quality Assurance program.

If you have any questions, contact me.

Sincerely,

Susan L. Kirshner -S

Digitally signed by Susan L. Kirshner -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300194629, cn=Susan L. Kirshner -S
Date: 2016.03.18 13:45:28 -04'00'

Susan Kirshner, Ph.D.
Review Chief
Division of Biotechnology Review and Research III
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 761033
Teva Respiratory LLC
Reslizumab

We refer to your March 30, 2015, BLA submission for reslizumab. We also refer to your labeling submission dated March 15, 2016. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert (PI) and Patient Package Insert (PPI). The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments may be forthcoming.

We request a response by COB March 18, 2016. If you have any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosures: FDA Proposed Prescribing Information and Patient Labeling

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

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/s/

COLETTE C JACKSON
03/17/2016

BLA 761033
Teva Respiratory LLC
Reslizumab

We refer to your March 30, 2015, BLA submission for reslizumab. We also refer to your labeling submission dated March 2, 2016. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert (PI) and Patient Package Insert (PPI). The FDA-proposed insertions are underlined and deletions are in strike-out. The rationale for some of the changes made in the package insert are outlined below; others are included within the PI and PPI. Our comments and recommendations are not all-inclusive and additional comments may be forthcoming.

1. **Section 5 - Warnings and Precautions (5.3 Malignancy)**

(b) (4) We do not agree with inclusion of this statement, as it does not reasonably qualify the information about malignancies and may be misleading because the data suggests a malignancy signal (i.e. double the incidence of malignancies in the CINQAIR group compared to the placebo group). Our final position is that this statement should be removed based on the premise that it is misleading [see 21 CFR 201.56(a)(2)].

2. **Section 6 – Adverse Reactions (Malignancy as an adverse drug reaction)**

A) The Issue of a Causal Relationship

(b) (4) However, this is not the regulatory standard for including untoward events in the ADVERSE REACTIONS section. According to the ADVERSE REACTIONS regulations [21 CFR 201.57(c)(7)] "for the prescription drug labeling, an adverse reaction is an undesirable effect, *reasonably associated with use of a drug*, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events *for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event*." Therefore, (b) (4) there only needs to be some basis to believe that there is a causal relationship. A doubling of the incidence of an event in the drug group compared to the placebo group can by itself meet the regulatory standard for inclusion as an adverse reaction in the

ADVERSE REACTIONS section. Additionally, a possible immunosuppressive role of IL-5 antagonists supports the inclusion of malignancy as an adverse drug reaction.

(b) (4) is not the regulatory standard for including adverse events in Section 6 (as outlined above), the imbalance in malignancies in the placebo controlled trials represents an empirical observation, not a theoretical concern, and thus provides a sufficient basis for determination of causality (1).

(b) (4)

- The timing of the event relative to the time of drug exposure: Most of the malignancies in the placebo-controlled trials were detected within the first six months of treatment. (b) (4) members of the Advisory Committee (Dr. Steve Georas, a noted expert in eosinophil biology) did not "view the early onset of cancers that patients were previously diagnosed with as a way of exonerating the drug. In some ways, if we think eosinophils are involved in tumor surveillance, I don't think that that should give us reassurance."
- Occurrence at a frequency above that expected in the treated population: (b) (4) the malignancy rate in patients treated with reslizumab was higher than what has been observed in the SEER (Surveillance Epidemiology and End Results) database (see Table 90, ISS). Advisory Committee member Dr. Brittain specifically objected to analyses excluding the early onset cases, expressing her confusion regarding the logic of excluding these cases in a setting where we are interested in knowing all the background. No atypical malignancies: Plasmacytoma is an exceedingly rare tumor (2), and yet a case of plasmacytoma occurred in a reslizumab treated patient (ISS Table 87).
- Lack of evidence of carcinogenicity in nonclinical studies: Data from nonclinical studies generally are not viewed as persuasive evidence against a causal link once an imbalance has been observed directly in controlled human trials.
- Immunosuppression – Failure to systematically capture evidence of opportunistic infections is not the same as the absence of an immunosuppressive safety signal. Similar programs have viewed all infections, including opportunistic infections, as adverse events of special interest meriting dedicated safety reporting (3).
- Extent of dose-response – All of the treatment emergent malignancies occurred on the 3 mg/kg dose, and none on the 0.3 mg/kg dose (ISS, Table 85). (b) (4)

Advisory Committee members commented specifically on the malignancy signal, consistent with fairly broad concern for a causal link (4). Some of the specific concerns/comments are summarized here:

- Dr. Georas: "As we move these compounds into the human population and look at years potentially of therapy, I personally am concerned about a cancer risk."

- Dr. Connett cited a paper entitled "Inverse association of eosinophil count with colorectal cancer" and said he found that "The strength of the evidence is fairly strong."
- Dr. Connett: "And if somebody is going to be taking this for a long time, which I would expect, there's going to be substantial risk, if the epidemiologic data is true, of at least colon cancer, possibly other cancers."

(b) (4) "Presentation of Less Common Adverse Reactions" heading [Section III(B)(4); Page 5] and under the "Selecting Adverse Events for Inclusion" heading [Section IV(A); Page 8] in the 2006 *Adverse Reactions Section of Labeling* guidance. (b) (4) this guidance states that less common adverse events should be included in the ADVERSE REACTION section if "there is *some* basis to believe there is a causal relationship between the drug and the event." Both of these headings in the guidance do not state that (b) (4) rather, this guidance states that only some of the factors should be present for an untoward event to be included in this section. It is likely that for the overwhelming majority of adverse reactions listed in the ADVERSE REACTIONS section of the prescribing information for all human prescription drug and biological products, all or most of these factors are not present. (b) (4)

In conclusion, consistent with the PLR Guidance it is the final position of the Division that malignancy should be included in the ADVERSE REACTIONS section. (b) (4)

3. Section 17 – Patient Counseling Information (Malignancy)

According to the *Patient Counseling Information section of labeling* guidance, this section "summarizes important adverse reactions and other risks to convey to patients. Information should typically include, as appropriate, the identification of the risk, management recommendations that are pertinent to patients, self-monitoring information, and information on when to contact a health care provider, seek emergency help, or discontinue the drug." Although there are no management recommendations in the Warnings & Precautions pertinent to patients, malignancy clearly is an important adverse reaction and should be included in the PATIENT COUNSELING INFORMATION section. Given that the review team and Teva both agree that malignancy should be in the W&P and a malignancy risk would be very important to patients, it is essential to include this possible risk in the PATIENT COUNSELING INFORMATION section.

Inclusion of this information in Section 17 provides patients with an opportunity to mitigate this risk by raising any concerns about a personal or family history of malignancy with their providers so as to make a fully informed choice before initiating reslizumab therapy. The short time to onset of malignancy observed in your program does suggest the possibility of

interference with tumor surveillance, which would be especially pertinent for patients with a personal or family history of malignancy. Informed patients may approach their own medical issues differently (e.g. an aggressive approach to cancer screening or ensuring that malignancy is considered in the differential diagnosis for any new complaints that may emerge after initiating treatment with reslizumab).

We request a response by COB March 15, 2016. If you have any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosures: Annotated and Unannotated Prescribing Information and Patient Labeling

REFERENCES

1. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; 58: 295-300.
2. Soutar R, Lucraft H, Jackson G, Reece A, Bird J, Low E, Samson D, Guidelines Working Group of the UKMF, British Committee for Standards in H, British Society for H. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *Br J Haematol* 2004; 124: 717-726.
3. FDA Briefing Information for the June 11, 2015 Meeting of the Pulmonary-Allergy Drugs Advisory Committee. 2015. p. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM450245.pdf.
4. Transcript for the December 9, 2015 Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) 2015. p. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM487402.pdf.

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/s/

COLETTE C JACKSON
03/10/2016

PeRC Meeting Minutes
February 10, 2016

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Linda Lewis
Ikram Elayan
Thomas Smith
Daiva Shetty
Meshaun Payne
Dianne Murphy
Gerri Baer
Rosemary Addy Non-Responsive
Wiley Chambers Non-Responsive
Julia Pinto
Maura O'Leary
Lili Mulugeta
Freda Cooner
Peter Starke
Gil Burckart
Raquel Tapia
Greg Reaman
Dionna Green
Lisa Faulcon Non-Responsive
Adrienne Hornatko-Munoz Non-Responsive
Barbara Buch
Rachel Witten
Michelle Roth-Kline
George Greeley

Reference ID: 3893195

Agenda

Non-Responsive

11:20	BLA 761033	Cinqair (reslizumab) Partial Waiver/Assessment (w/agreed iPSP)	DPARP	Colette Jackson	For add-on maintenance treatment of patients with severe asthma aged 18 years and older, with an eosinophilic phenotype

Non-Responsive

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Non-Responsive

Cinqair (reslizumab) Partial Waiver/Assessment (w/agreed iPSP)

- Proposed Indication: An interleukin 5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
- The product triggers PREA as a new active ingredient and has a PDUFA Goal date of March 28, 2016.
- The division clarified that this product is administered as an IV injection (b) (4) This product was recently reviewed at a Pulmonary-Allergy Drugs Advisory Committee meeting. The division noted concerns regarding the lack of efficacy of the product in patients 12-17 years of age. The AC voted 14-0 against approval of this IV product. (b) (4)
- (b) (4)
- *PeRC Recommendations:*
  - The PeRC agreed with the Division's plan to waive studies of the IV formulation patients less than 12 years of age because the product would be ineffective and also agreed that the assessment in patients 12 to 17 years of age as studies is complete. (b) (4)

Non-Responsive

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/s/

MESHAUN L PAYNE
02/26/2016

BLA 761033
Teva Respiratory LLC
Reslizumab

We refer to your March 30, 2015, BLA submission for reslizumab. We also refer to your labeling submission dated February 17, 2016. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments may be forthcoming.

We request that you submit revised prescribing information labeling by the close of business on March 2, 2016. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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/s/

COLETTE C JACKSON
02/26/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

2/18/16

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following request for information. We request a written response by February 22, 2016 in order to continue our evaluation of your application.

Please update the (b) (4) bioburden limits in Section 3.2.S.2.4 (b) (4) as committed in amendment dated 11/24/2015.

If you have any questions, please contact Andrew Shiber, Regulatory Business Process Manager, at (301)796-4798 or Andrew.Shiber@fda.hhs.gov.

Sincerely,

Anita N. Brown -S

Digitally signed by Anita N. Brown -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anita N. Brown -S, 0.9.2342.19200300.100.1.1=2000546085
Date: 2016.02.18 12:02:54 -05'00'

Anita N. Brown
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 761033
Teva Respiratory LLC
Reslizumab

We refer to your March 30, 2015, BLA submission for reslizumab. We are providing FDA recommendations and comments in the attached labeling for the proposed Package Insert. The FDA-proposed insertions are underlined and deletions are in strike-out. Our comments and recommendations are not all-inclusive and additional comments will be forthcoming. FDA comments and recommendations for the proposed Patient Package Insert will be provided in a separate labeling correspondence.

We also refer to your submission dated January 29, 2016, which provided draft carton/container labeling for FDA consideration. We have reviewed the submission and have no objections to your proposed carton/container labeling.

We request that you submit revised carton/container labeling and provide your response to our FDA package insert labeling by the close of business on February 17, 2016. If there are any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

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/s/

COLETTE C JACKSON
02/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

2/5/16

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following request for information. We request a written response by February 9, 2016 in order to continue our evaluation of your application.

Refer to your correspondence dated January 19, 2016 where your provided information about an extractable study of the (b) (4) . Provide the following information:

1. (b) (4)
2.
3.

If you have questions, call me, at (301) 796-0906.

Sincerely,

Melinda J. Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300178565, cn=Melinda J. Bauerlien -S
Date: 2016.02.05 13:56:55 -05'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Your BLA 761033/0, submitted March 30, 2015, is under review. We have the following comments regarding your revised container label and carton labeling submitted on January 4, 2016.

A. General Comments

1. You note there will be a lot number printed on the aluminum ferrule. Confirm there is no text on the top of the ferrule to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals. Placement of text on the side of the ferrule is acceptable.

B. Carton Labeling

1. We note the following concerns with your manufacturer information:

    a. The Applicant/licensed manufacturer on the 356h form does not appear on the labeling. Thus, the labeling does not comply with 21 CFR 610.61(b).

    b. It appears as if the pending US License Number 2016 will be assigned to Teva Respiratory, LLC. (b) (4)

    c. (b) (4) a contract manufacturer, is not required on the labeling.

Teva (b) (4) is the Applicant (b) (4) The licensed manufacturer is responsible for ensuring the manufacture of the product complies with the provisions of the BLA and applicable regulations. Contract facilities are considered to be under the control of the license holder, specific identification of the contractor in the product labeling is not required. Refer to Guidance for Industry Cooperative Manufacturing Arrangements for Licensed Biologics, with specific regard to Contract Manufacturing Arrangements. (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm069908.pdf)

For CDER-regulated BLAs, the manufacturer information must appear as "Manufactured by: the Applicant, name address, license number" to fulfill 21 CFR 610.61(b).

Manufactured by:
Teva (b) (4)
Frazer PA 19355
U.S. License Number 2016

The distributor can appear on the label provided the licensed manufacturer name, address, and U.S. License Number appears per 21 CFR 610.64.

If you want to display additional manufacturer information, cite the regulation(s) that you are attempting to fulfill.

C. Vial Container Label

1. Revise the manufacturer information to comply with 21 CFR 610.60(a)(2). The manufacturer information should appear as:

    Manufactured by:
    Teva (b) (4)
    Frazer PA 19355
    U.S. License Number 2016

In order to facilitate the review of your submission, provide the requested information by January 29, 2016. You may submit your response via telephone facsimile at 301-796-9728, or by email to Colette.Jackson@fda.hhs.gov, followed by an official submission to your BLA.

Review/History Clearance From

Drafted by: L. Musse	Date: 1/22/16
Clearance: S. Barnes	Date: 1/22/16
Finalized: L. Musse	Date: 1/22/16
File Name: C&C IR	Date: 1/22/16

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/s/

LAURA MUSSE
01/22/2016

BLA 761033
Reslizumab
Teva

Your submission dated March 30, 2015, to BLA 761033 is currently under review. We have the following requests.

Provide your agreement to conduct the following Post Marketing Requirements (PMR) and provide the final report submission date for each listed below.

PMR #1: Develop and validate an assay that is sufficiently sensitive, selective, and specific to reliably detect product specific antibodies of the IgE isotype.

Final report submission date: **Insert Date**

PMR #2: Use the anti-reslizumab IgE assay developed under PMR #1 to test serum samples from patients who had treatment associated anaphylaxis.

Final report submission date: **Insert Date**

PMR #3 Submit a qualification report demonstrating the suitability of the commercial anti-alpha gal ELISA from (b) (4) that was used to analyze the sera of the four treatment-related anaphylaxis patients.

Final report submission date: **Insert Date**

Provide your commitment to conduct the following and provide the final report submission date for each listed below. For PMCs that are time sensitive, we have proposed final report submission dates.

PMC #1: Develop and validate an assay to detect anti-drug antibodies that neutralize reslizumab activity. The assay should be sufficiently sensitive, selective, and specific to reliably detect neutralizing anti-drug antibodies.

Final report submission date: **Insert Date**

PMC #2: To use the assay developed and validated under PMC 1 to detect anti-reslizumab neutralizing antibodies in sera from confirmed anti-drug antibody positive asthmatic patients.

Final report submission date: **Insert Date**

PMC #3: To implement a (b) (4) in the drug substance manufacturing process. The final study report(s) will be submitted according to 21 CFR 601.12.

Reference ID: 3872150

Final report submission date: **April 2016**

PMC #4 Re-evaluate and tighten the (b) (4) endotoxin acceptance criteria for the (b) (4) samples after manufacturing 30 batches of reslizumab.

Final report submission date: **Insert Date**

PMC #5: Establish a hold time limit for the intermediate (b) (4) These hold times should be validated at scale to demonstrate that these (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.

Final report submission date: **Insert Date**

PMC #6: To develop, validate and establish an identity test for incoming bulk drug substance to the drug product manufacturing site that uniquely confirms identity of reslizumab. The final study report(s) will be reported according to 21 CFR 601.12

Final report submission date: **Insert Date**

PMC# 7: To reduce the vial over fill to comply with USP <1151> recommendations. Provide information to demonstrate fill consistency at the revised volume. The final study report(s) will be reported according to 21 CFR 601.12

Final report submission date: **Insert Date**

PMC #8: Requalify the dye ingress container closure integrity (CCI) test method with reslizumab 10 mL/20 mm vial under worst case challenge conditions using positive controls with a breaches of ≤ (b) (4) µm in size and submit the data in accordance with 21 CFR 601.12.

Final report submission date: **April 2016**

PMC #9: Qualify the microbial retention study at routine manufacturing /room temperature and submit the results in accordance with 21 CFR 601.12.

Final report submission date: **June 2016**

PMC #10: To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from

Reference ID: 3872150

at least thirty released lots of reslizumab drug substance and drug product. The final study report(s) will be submitted according to 21 CFR 601.12.

Final report submission date: **Insert Date**

PMC #11: To improve the overall control strategy of the drug substance manufacturing process (b) (4)

Final report submission date: **Insert Date**

In order to facilitate the review of your submission, provide the requested information by January 18, 2016. You may submit your response via telephone facsimile at 301-796-9728, or 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.

Drafted:	Colette Jackson/ January 8, 2016
Initialed:	Sandy Barnes/ January 8, 2016 Maria-Teresa Gutierrez-Lugo/ January 11, 2016 Sally Seymour/ January 12, 2016
Finalized:	Colette Jackson/ January 12, 2016

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/s/

COLETTE C JACKSON
01/12/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

12/23/15

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB January 5, 2016.

1. The release and stability (b) (4) specifications for reslizumab drug substance and drug product provides quantitative acceptance criteria for monitoring and controlling the following (b) (4) . Revise your (b) (4) specification to include additional acceptance criteria (b) (4) Provide the revised (b) (4) specifications along with a justification to support the proposed additional acceptance criteria.

Sincerely,

Maria Teresa Gutierrez Lugo -S

Digitally signed by Maria Teresa Gutierrez Lugo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S
Date: 2015.12.23 16:08:22 -05'00'

Maria-Teresa Gutierrez-Lugo
Lead Chemist
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

LABELING PMR/PMC DISCUSSION COMMENTS

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We also refer to our June 11, 2015, letter in which we notified you of our target date of December 23, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "Biosimilar Biological Product Authorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On July 27, 2015, we received your July 27, 2015, revised proposed labeling submission to this application, and we have the following comments. We also refer you to the December 14, 2015, telephone conversation with your company outlining our labeling revisions. We request that you resubmit labeling that addresses the comments below and those discussed during our telephone conversation by January 4, 2016. The resubmitted labeling will be used for further labeling discussions.

Container and Carton Labeling Comments

A. General Comments

1. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

2. Confirm there is no text on top of the ferrule and cap overseal of the vials to comply with United States Pharmacopeia (USP) General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

B. Carton Labeling

1. Delete or decrease the size of the graphic on the principal display panel (PDP), located above the proprietary name to increase the white space on the label to improve readability per 21 CFR 201.15. As currently presented, the PDP is cluttered which may affect readability of pertinent information.

2. Replace "Tradename" with conditionally accepted proprietary name, Cinqair, throughout all labels and labeling.

3. Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name.

4. Present the names on the carton per display below.

   Cinqair
   (reslizumab)
   Injection

   Ensure the proper name is at least half the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

5. Revise the strength presentation by including the strength per milliliter (mL) in accordance with USP General Chapter <1>. Ensure the strength per total volume is more prominent than the strength per mL. For example:

   100 mg/10 mL
   (10 mg/mL)

6. Revise the statement [redacted] (b) (4)" to "For Intravenous Infusion Only Dilute Prior to Administration". We recommend this to minimize the risk of administering the drug as an intravenous bolus.

7. Revise "Single-Use Vial" to read "Single-Dose Vial". The Agency recommends consistent use of the appropriate package terms and discard statements. See the Agency's current thinking on this issue (FDA Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf)

8. Place "One Single-Dose Vial" before the "Discard Unused Portion" statement to maintain consistency with other labels and labeling.

9. Revise the statement of ingredients to comply with with USP General Chapters: <1091> Labeling of Inactive Ingredients. For example:
   Each mL contains 10 mg reslizumab, glacial acetic acid (0.12 mg), sodium acetate trihydrate (2.45 mg), and sucrose (70mg).

10. Add a warning to prevent shaking. For example, revise the storage statement to read "Store in refrigerator at 2ºC - 8ºC (36°F - 46°F) in original carton to protect from light. Do not freeze. Do not shake."

11. Delete the statement "(b) (4)

12. Revise the statement (b) (4) to read "Sterile. No preservative." To comply with 21 CFR 610.61(e).

13. Add the statement "No U.S. standard of potency" to comply with 21 CFR 610.61(r).

14. Revise the manufacturer information to comply with 21 CFR 610.60(a)(2). The manufacturer information should appear as:

    Manufactured by:
    Teva (b) (4).
    Frazer PA 19355
    U.S. License Number 2016

    If you want to display additional manufacturer information, cite the regulation that you are attempting to fulfill.

C. Vial Container Label

1. See comments B2, B3, B4, B5, B6, B7.

2. Revise "Single-Use Vial" to read "Single-Dose Vial. Discard Unused Portion."

3. Add the statement "Usual Dosage: see insert" to comply with 21 CFR 201.55.

4. Revise the storage statement to read "Store at 2ºC - 8ºC (36°F - 46°F) in original carton to protect from light. Do not freeze. Do not shake."

5. Revise the manufacturer information to comply with 21 CFR 610.60(a)(2). The manufacturer information should appear as:

   Manufactured by:
   Teva (b) (4)
   Frazer PA 19355
   U.S. License Number 2016

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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/

COLETTE C JACKSON
12/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

12/7/15

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your application. Please submit your response to questions 1 to 3 prior to COB December 22, 2015 and response to question 4 prior COB January 13, 2015.

1. In your information request response dated 07th December 2015, you provided inadequate additional acceptance criteria (b) (4) (b) (4)

2. (b) (4) Please clarify whether you are requesting approval of the post-approval stability protocols defined in sections 3.2.S.7.2 and 3.2.P.8.2. (b) (4)

3. We note that you recently amended your BLA submission (b) (4) Revise your post-approval stability protocol for drug product (b) (4)

4. The preparation and administration instruction of your proposed labeling indicates that your product is "compatible with polyvinylchloride (PVC) or polyolefin infusions bags". The in-use compatibility data for the polyolefin infusion bags included two studies (study 1a and 2a of Table 1 of section 3.2.P.2.6). These studies did not include evaluation of potency, sub-visible particles, (b) (4) . In addition, the studies did not evaluate reslizumab infusion preparations relevant to low and high body weight of the treatment populations and did not evaluate the product at 2-8 °C. To support the compatibility of your product with the polyolefin infusion bag, provide potency, sub-visible particles, (b) (4) data. Data to support reslizumab infusion preparations relevant to low and high patient body weight, and storage temperatures described in your product labeling should also be provided. You may use a similar experimental design as the one conducted for study 3 of Table 1 of Section 3.2.P.2.6. Also submit in your report representative raw data from the (b) (4) results from the completed study 3 and the study conducted to support the use of polyolefin infusion bag. Alternatively, in lieu of providing these study results, you may remove the use of the polyolefin bag from the product labeling.

Sincerely,

Maria Teresa Gutierrez Lugo -S

Digitally signed by Maria Teresa Gutierrez Lugo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=00118188863, cn=Maria Teresa Gutierrez Lugo -S
Date: 2015.12.17 16:52:23 -05'00'

Maria-Teresa Gutierrez-Lugo
Lead Chemist
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

12/11/15

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB December 15, 2015.

1. Your proposed release specifications for drug substance (DS) and drug product (DP) are not supported by your clinical and manufacturing experience. In addition, we note that several safety signals were observed in the reslizumab clinical studies. The mechanisms underlying these safety signals and their potential relationship with product quality attributes remain unclear. Therefore, you should revise the DS and DP acceptance criteria for the following test methods to align with your clinical experience from pivotal studies:

   (a) For potency, the proposed acceptance criteria for DS and DP are (b) (4)% of the reference standard. These criteria are (b) (4) your clinical experience. The potency of clinical lots, and from lots manufactured using the (b) (4)L commercial process and measured by the current (b) (4) assay, ranged between (b) (4)% for DS and (b) (4)9% for DP.

   (b) For (b) (4), the proposed acceptance criteria for DS and DP are ≥ (b) (4)% of (b) (4). For (b) (4) the proposed acceptance criteria for DS and DP are ≥ (b) (4)% of (b) (4) and ≤ (b) (4)% (b) (4) These criteria are not reflective of clinical and at-scale manufacturing experience. We note that the following ranges were observed for DS and DP– for (b) (4) all pivotal clinical lots were above (b) (4)% of (b) (4)

[redacted]; for non-reduced cSDS all the pivotal clinical lots were above [redacted]% of [redacted] and [redacted]% [redacted]

(c) For [redacted] the proposed acceptance criteria for DS and DP are: [redacted] We note that the following ranges were observed from your clinical and manufacturing experience – [redacted]% for DS and [redacted] for DP, [redacted]: [redacted]% for DS and [redacted] for DP, and [redacted]: [redacted]% for DS and [redacted] for DP.

(d) For [redacted], the proposed acceptance criteria for DS and DP are ≥ [redacted]% [redacted] and ≤ [redacted]% [redacted] The observed [redacted] levels were consistently in the range of [redacted]% for both DS and DP.

(e) For the [redacted] impurity, the proposed acceptance criteria for DS are ≥ [redacted] ng/mg [redacted]. The levels [redacted] in your commercial and pivotal clinical material ranged between [redacted] ng/mg [redacted]

(f) In response to an information request dated Dec2, 2015, you propose to update the acceptance criteria for the DP specification- Appearance, Visible Particle Matter from [redacted] to "May contain translucent to white, amorphous proteinaceous particles". In addition to implementing this proposed update, revise your acceptance criteria to also specify that the product should be free from foreign material.

2. In your BLA, you propose to include both [redacted] testing sites for [redacted] testing of reslizumab DS by the [redacted] method. You provided a study report (ESPI-11776) in support of the transfer of the [redacted] assay [redacted] Your assay transfer evaluation was conducted with [redacted] samples, [redacted] In addition to the difference [redacted] were different. Therefore, since the assay was not properly transferred, you should remove [redacted] testing by [redacted] method from the testing responsibilities [redacted]

3. In a response to Information Request dated 04th December 2015, you provided information [redacted]

[redacted] (b) (4) This is not acceptable. [redacted] (b) (4) . Implement an [redacted] (b) (4) that is supported by process validation studies and available data from at-scale batches demonstrating clearance of this impurity.

4. We note that the [redacted] (b) (4) container used for reslizumab DS is composed of [redacted] (b) (4) [redacted] Provide a risk assessment on the use of [redacted] (b) (4) container system for reslizumab DS with regards to the potential impact from [redacted] (b) (4) [redacted] leachable.

5. In Section 3.2.R. Regional Information of your BLA, you provided an incorrect SOP for [redacted] (b) (4) assay. Update your BLA with the correct SOP for in [redacted] (b) (4) assay.

6. The post-approval stability protocol and stability commitment sections (3.2.S.7.2 and 3.2.P.8.2) do not specify whether you intent to submit data from the stability studies to the Agency. Revise sections 3.2.S.7.2 and 3.2.P.8.2 to specify commitments to submit the data from all ongoing stability studies and the data from annual stability lots in the BLA annual reports.

7. In a response to Information Request dated 07th December 2015, you provided information on the stability assessment of the working reference standard. Your proposed stability acceptance criteria are inadequate [redacted] (b) (4) [redacted] Revise your working reference standard protocol [redacted] (b) (4) [redacted].

8. You provided data on the characterization of the levels of [redacted] (b) (4) for batch 202709ARS in your BLA submission. Provide data on the levels [redacted] (b) (4)

[redacted] in reslizumab throughout development, including batches used in clinical studies that you intend to use to support your application. In addition describe your control strategy for relative levels [redacted] in your product.

9. In your response to an Information Request dated 07th December 2015, you propose to update the [redacted] protocol to include current release DS acceptance criteria. This approach would be acceptable provided the DS release acceptance criteria are revised as described in comment 1 above. However, your proposal [redacted] is not acceptable. [redacted]

Sincerely,

Maria Teresa Gutierrez Lugo -S

Digitally signed by Maria Teresa Gutierrez Lugo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=001181863, cn=Maria Teresa Gutierrez Lugo -S
Date: 2015.12.11 16:13:19 -05'00'

Maria-Teresa Gutierrez-Lugo
Lead Chemist
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

12/3/15

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

INFORMATION REQUEST

Teva Branded Pharmaceutical Products R&D, Inc.
Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs
41 Moores Road
PO Box 4011
Frazer, PA 19460

Dear Ms. Kampf:

Please refer to your original Biologics License Application received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We are reviewing your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your application. Please submit your response prior to COB December 7, 2015.

In comments 2 and 3 of the information request dated December 2, 2015, we requested revision of the (b) (4) In addition to the revisions requested in comments 2 and 3, we request that you address the following:

1. (b) (4)

2.

Sincerely,

Maria Teresa Gutierrez Lugo -S

Digitally signed by Maria Teresa Gutierrez Lugo -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011818863, cn=Maria Teresa Gutierrez Lugo -S
Date: 2015.12.03 12:07:33 -05'00'

Maria-Teresa Gutierrez-Lugo
Lead Chemist
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 761033
Reslizumab

Your submission dated March 30, 2015, to BLA 761033 is currently under review. We have received your response dated October 5, 2015, to the Information Request issued on September 24, 2015, and have the following comments and/or additional request(s) for information:

1. The table provided in response to item 1 addresses the latter portion of the Agency's request, however, the syntax submitted October 5, 2015, references a derived dataset, 'D_CPK.' Send one executable syntax file that will generate the requested CPK table **from the datasets submitted with your BLA**, i.e. inclusive of the syntax necessary to derive the 'D_CPK' dataset, presumably from the ISS14 DDLB dataset.

2. Investigate the CPK safety signal for drug-drug interactions. Include specific analyses for oral corticosteroids, statins, anti-epileptics and other drugs known to contribute to toxic myopathies. In addition, perform an exploratory analysis for novel potential drug-drug interactions.

We request your reply ASAP or by COB, Tuesday, October 13, 2015. If you have any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Reference ID: 3830874

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/s/

COLETTE C JACKSON
10/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

MID-CYCLE COMMUNICATION

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Reslizumab.

We also refer to the teleconference between representatives of your firm and the FDA on September 8, 2015. 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

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 8, 2015, 4PM to 5 PM EST

Application Number: BLA 761033
Product Name: Reslizumab
Indication: Asthma
Applicant Name: Teva Pharmaceuticals

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

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Badrul A. Chowdhury, M.D., Ph.D., Director,
Lydia Gilbert-McClain, M.D., Deputy Director
Banu Karimi-Shah, M.D., Clinical Team Leader
Kathleen Donohue, M.D., Clinical Reviewer
Carol Galvis, Ph.D., Pharmacology/Toxicology Reviewer
Marcie Wood, Ph.D., Pharmacology/Toxicology Supervisor
Peter Starke, M.D., Associate Director, Labeling
Colette Jackson, Senior Regulatory Health Project Manager

Office of Product Quality, Office of Biological Products
Amy Rosenberg, M.D., Director
Susan Kirshner, Ph.D., Team Leader
Maria Gutierrez Lugo, Ph.D., Supervisor
Ramesh Potla, Ph.D., Product Reviewer
Tracy Denison, Ph.D., Product Reviewer
Joao Pedras-Vasconcelos, Ph.D., Immunogenicity Reviewer

Office of Product Quality, Office of Process and Facilities
Patricia Hughes, Ph.D., Supervisor
Lakshmi Narasimhan, Ph.D., Microbiology Reviewer
Bo Chi, Ph.D., Microbiology Reviewer

Office of Biometrics, Division of Biometrics II
David Petullo, M.S., Team Leader
Lan Zeng, Ph.D., Biostatistics Reviewer

Division of Clinical Pharmacology II, Office of Clinical Pharmacology
Yunzhao Ren, PhD,

EASTERN RESEARCH GROUP ATTENDEES
Christopher A. Sese, Independent Assessor
Peggah Khorrami, Independent Assessor

TEVA PHARMACEUTICALS ATTENDEES

Christine Kampf, Associate Director, Regulatory Affairs
Kenneth Bonk, Sr. Director, Regulatory Affairs
Brittany Bentz, Associate, Regulatory Affairs
Tushar Shah, M.D., Sr. VP Global Respiratory R&D
James Zangrilli, M.D., Sr. Director, Clinical Project Leader
Yael Shalit, M.D., Director, Pharmacovigilance Safety Physician
Judith Zander, M.D., Global Head of Safety Physicians
Laurie Pukac, Ph.D., Director, Global Bioassays and Technology
Linglong Zou, Ph.D., Director, Experimental Immunology and Global Bioassays and Technology
Barbara Butler, MS, MBA, Associate Director, CMC Project Management, Biologics R&D
Ping Feng, MS, Head of Analytical Sciences, Global Biological CMC
Jason Bock, Ph.D., VP, Global CMC Biologics
Sivan Weiss, MSc, Associate Director, Global Biostatistics
Mary Bond, MS, MBA, Director, Clinical Pharmacology
Mary Peterman, Pharm.D., MBA, Sr. Director, Project Champion

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.

A Mid-Cycle Communication agenda was sent to Teva on September 3, 2015. Teva sent a points of clarification document via email on September 8, 2015, which was submitted officially to the BLA on September 11, 2015.

Reference ID: 3831479

2.0 SIGNIFICANT ISSUES

- *As communicated in the filing letter, the lack of evidence for a reduction in exacerbations is noted for the following key subgroups: patients 12 to 17 years of age, black patients, and US patients. This remains a review issue.*

Meeting Discussion:

Teva stated that they have looked at other measures beyond FEV1 and will provide additional analyses and information to the Agency.

- *Concerns regarding the large number of protocol violations, the timing of protocol amendments relative to enrollment, the misclassification of a stratification variable, and the timing of database finalization relative to unblinding have not been resolved and remain significant review issues.*

Meeting Discussion:

Teva acknowledged the comment and noted they are confident in their study conduct and assured that the conclusions will not be impacted by the issues raised.

- *An information request will be sent to request data on the neutralizing capacity of the anti-drug antibodies detected in patient samples that confirm positive as well as validation report for the neutralizing antibody assay used to test these samples.*

Meeting Discussion:

Teva referred to their points of clarification document for this FDA comment which outlined their rationale for not having a validated neutralizing assay to test their Phase III clinical samples, (b) (4) The FDA stated that their response requires further Agency review however, their justification as outlined is preliminarily unacceptable. The FDA will provide an information request communication to Teva regarding this issue.

- *A satisfactory evaluation of all manufacturing facilities is required for BLA approval.*

Meeting Discussion:

The Agency reminded Teva that a satisfactory evaluation of all manufacturing facilities is required for BLA approval, especially the (b) (4) facility which had a pre-license inspection for reslizumab recently. Teva acknowledged the comment and stated that they understand the comment.

Reference ID: 3831479

3.0 INFORMATION REQUESTS

To date we have communicated two CMC information requests:

- *On August 24, 2015, we requested information on microbial and endotoxin control of reslizumab drug substance and drug product, including process validation and the container closure integrity test for reslizumab drug product. We requested response to this information request prior to September 11, 2015.*

Meeting Discussion:

Teva noted that they are on target to respond to our FDA information request by September 11, 2015.

- *On July 13, 2015, we requested information on process validation of reslizumab drug substance and revision of the facilities listed in the application 356h form. We received response to this information request. The data are currently under review.*

Meeting Discussion:

There was no discussion for this FDA response.

4.0 MAJOR SAFETY CONCERNS

- *We note the higher rate of anaphylaxis in patients treated with reslizumab compared to those treated with placebo. In an information request dated September 3, 2015, we have requested a more detailed clinical analysis of potential anaphylaxis cases using NIAID/FAAN criteria.*

Meeting Discussion:

Teva revealed that they may not have pertinent information available beyond what is already in the safety database. For example, key details such as time of adverse event were not recorded in the case report forms. As detailed medical records surrounding an adverse event were not captured systematically in Teva's program, it will not be feasible to generate a narrative report based on review of the available records. Given the significant limitations in Teva's safety database, the Division agreed to the tabular reporting format proposed by Teva, but requested that narratives be provided if any additional pertinent information is available.

Reference ID: 3831479

The Division did not agree to Teva's proposal to exclude the terms (b) (4) from the anaphylaxis SMQ. The standard, broad, complete MedDRA query for anaphylaxis should be performed as the primary analysis, with no exclusion of terms.

Post-Meeting Comment and Request for Information

Provide both a SAS.XPT and PDF version of the tabular format report. Provide a sensitivity analysis of the anaphylaxis SMQ without the asthma and cough terms. This will be reviewed in addition to the primary analysis in order to better characterize the overall safety signal.

- *An information request will be sent to request the development of a sensitive and product-specific IgE antibody assay and analysis of sera samples from patients who developed anaphylaxis. This information is needed because we are concerned that episodes of anaphylaxis may be triggered by anti-drug IgE antibodies in susceptible patients. Although your three confirmed patients were reportedly anti-drug antibody negative, your screening antibody assay has a sensitivity of 22 ng/ml; which is insufficient to detect clinically relevant IgE. Typically a sensitivity below 5 ng/ml is needed in order to detect clinically relevant IgE.*

Meeting Discussion:

(b) (4) The FDA stated Teva would need to make an effort as there are assays available to detect IgE antibodies below 5 ng/mL.

- *You provided data on the characterization of relative percentage of neutral glycans for batch 202709 ARS in your BLA submission.* (b) (4) *An information request will be sent to request characterization data on alpha-gal species in reslizumab throughout development, including batches used in the clinical studies that you intend to use to support your application.*

Meeting Discussion:

Teva asked the FDA why the concern regarding the presence of alpha-gal species. The FDA informed Teva that there is established literature, of which Teva is likely aware, as it related to the presence of alpha-gal in drug products. FDA also informed Teva that an information request regarding further characterization of alpha-gal in clinical drug lots is forthcoming.

- *CPK elevations are noted as a safety signal in your development program. Whether any cases meet the criteria for rhabdomyolysis is under review. An information request will be forthcoming soon requesting additional information for further evaluation of this safety signal.*

Meeting Discussion:

No discussion was held for this FDA comment.

5.0 RISK MANAGEMENT

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

Meeting Discussion:

No discussion was held for this FDA comment.

6.0 ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting to discuss this application is currently scheduled for December 9, 2015. Anticipated topics for discussion are outlined under Headings 2 and 3, Significant Review Issues and Major Safety Concerns, respectively.

Meeting Discussion:

No discussion was held for this FDA comment.

7.0 LATE-CYCLE MEETING

The Late Cycle Meeting is scheduled for November 23, 2015 as a Face to Face meeting.

Meeting Discussion:

No discussion was held for this FDA comment.

8.0 ATTACHMENTS AND HANDOUTS

The points of clarification document provided by Teva via email on September 8, 2015, and officially submitted to the BLA on September 11, 2015.

Reference ID: 3831479

1.12.4 Request for comments and advice

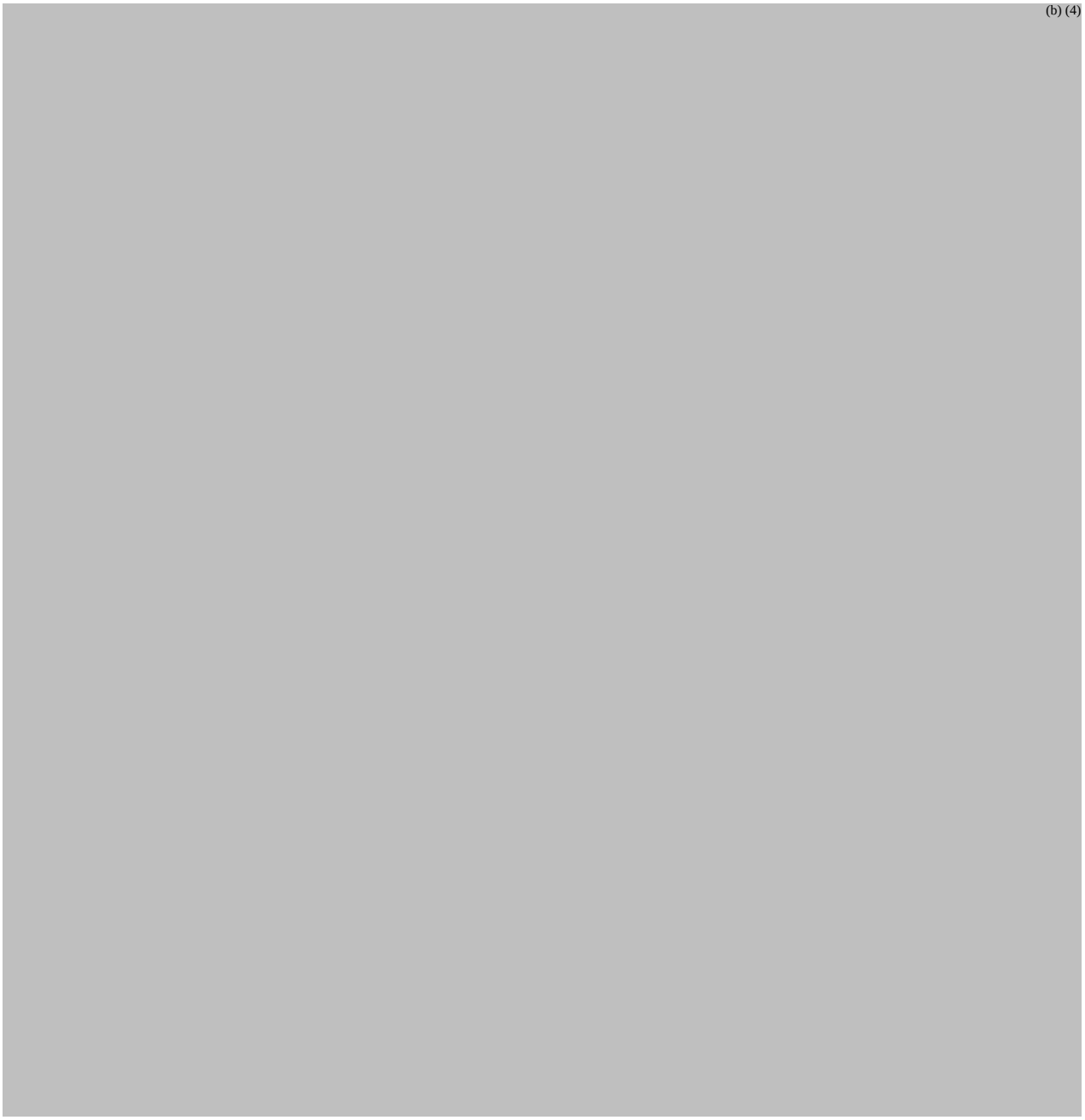
The following provides for clarifications and requests (bolded) for FDA agreement or comment based on the mid-cycle communication meeting agenda for the teleconference to take place between FDA and Teva on Tuesday, September 8, 2015 at 4:00 PM EST.

Under heading 3, Significant Review Issues, Teva has the following clarifications:

1. **FDA Comment, Bullet Point 3:**

   An information request will be sent to request data on the neutralizing capacity of the anti-drug antibodies detected in patient samples that confirm positive as well as validation report for the neutralizing antibody assay used to test these samples

   Teva Response:



Reference ID: 3831479

1.12.4 Request for comments and advice

As noted above, the NAb method validation reports used in early studies (assay qualification or validation reports, P6316 and 256-0904) have been submitted as part of the original BLA.

Given that:

1. all results of any neutralizing antibody assay used over the course of development of reslizumab have already been provided (along with the corresponding assay validation report) in the BLA,
2. beyond those previously noted, no neutralizing antibody assay was utilized (or validated) for further study with reslizumab,
3. the ADA detected in the clinical program with reslizumab using an assay which meets current regulatory standards did not show a signal of neutralizing capacity when viewed in light of blood eosinophil levels and efficacy,

Teva would like to confirm that no further action is required.

1.12.4 Request for comments and advice

Under heading 4, Major Safety Concerns, Teva has the following clarification:

1. **FDA Comment, Bullet Point 1:**

   We note the higher rate of anaphylaxis in patients treated with reslizumab compared to those treated with placebo. In an information request dated September 3, 2015, we have requested a more detailed clinical analysis of potential anaphylaxis cases using NIAID/FAAN criteria.

   Teva Response:

   In FDA's information request dated September 3, 2015, FDA has requested the following:

   1. ***Of the cases identified via the broad standard MedDRA query (SMQ) for 'Anaphylactic Reaction' in your integrated safety database, identify the subset with onset of reaction within 24 hours of study drug administration. Generate patient narratives for the subset of cases with onset of reaction within 24 hours of study drug administration. Once generated, submit these narratives for review.***

   Teva would like to provide the following clarifications/ request FDA agreement with Teva's approach:

   - Day and time of infusion was captured in database (DD/MM/YYYY and HH/MM); however, the onset of adverse events was only captured with the day the event started. There was no documentation of hour/minutes. Therefore, Teva will include in the requested summary all identified events occurring on the day of infusion (some of which may have occurred prior to administration of IV infusion) or the day following infusion. **Does the Agency agree with this approach?**

     Of note, in some of the serious cases we have information on the time to onset of the event in relation to study drug infusion; this includes the 3 currently identified, related anaphylaxis cases. Where exact timing is provided in our database, we will provide this in the narrative to be provided to FDA.

   - (b) (4)

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Reference ID: 3831479

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/s/

COLETTE C JACKSON
10/08/2015

BLA 761033
Reslizumab

Your submission dated March 30, 2015, to BLA 761033 is currently under review. We have the following comments and/or request(s) for information:

The myalgia and elevated CPK safety signal is a review issue. You have presented your data using The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Whether these are appropriate for grading of events in your program is a review issue. Therefore, we ask you to provide the information (as detailed below) using the standards outlined in the "Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" for evaluating and reporting laboratory abnormalities.

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
CPK	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN

1. Provide executable SAS syntax to generate the following table from the datasets submitted with your BLA. Use the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers. The syntax should be one file, inclusive of any macros. The table should reflect the single highest CPK value for each subject in the safety population over the course of their participation in the Reslizumab program. The number of observations in this table should sum to the number of participants in your safety population (Cohort 3). Include unscheduled visits, if applicable.

Max CPK per participant, safety population

	Reslizumab N (%)	Placebo N (%)
Normal (<1.25 ULN)		
Mild (Grade 1, 1.25 - 1.5 x ULN)		
Moderate (Grade 2, 1.6-3 x ULN)		
Severe (Grade 3, 3.1-10 x ULN)		
Potentially Life Threatening (Grade 4, > 10 x ULN)		
All		

2. Provide narratives (or hyperlinks to location within the BLA for previously submitted narratives) for patients:

- with serious adverse events, discontinuations, or temporary interruptions in study drug for adverse event from Musculoskeletal and Connective Tissue Disorders SOC or CPK elevations
- with CPK > 10 x ULN (severe or potentially life threatening for the healthy adult population)
- with HLT for myopathy, including patients 828411 and 630319

Reference ID: 3824337

- identified via the Teva-generated customized post-hoc analysis of myopathy adverse events (86 reslizumab patients and 57 placebo patients)
- with adverse events occurring within 24 hours after infusion in the Musculoskeletal and Connective Tissue Disorders SOC (23 reslizumab patients and 11 placebo patients)

3. Where possible, include in the narratives:
    - Total number of study drug doses received and overall treatment duration (in days) prior to the event
    - Time (in days) since last dose of study drug to onset of muscle symptom or CPK elevation
    - All CPK values for that participant over time, from baseline to end of study. A graph with reference lines for the normal range would be helpful.
    - Treatment arm
    - Pertinent history, such as muscle weakness or pain, discolored urine
    - Concomitant medications
    - Pertinent physical exam findings, such as wasting, weakness or tenderness
    - Pertinent laboratory findings, such as liver function tests, myoglobin, urine test strip (+) for blood, potassium, calcium, BUN, Cr, LDH etc.
    - Urine microscopy
    - Results from any muscle biopsies, EMGs, or other specialized clinical tests for muscle injury
    - Course of the adverse event – any hospitalizations, treatments needed, etc.
    - Whether patient continued on treatment
    - Outcome/resolution of any laboratory abnormalities or clinical symptoms

We acknowledge that the same limitations in the safety database identified for the anaphylaxis safety review may apply to this request, however, we ask that you provide as much detail as possible. If you intend to provide the data in tabular format, similar to what is planned for the anaphylaxis safety review, provide both a SAS.xpt version and a PDF version.

We request your reply ASAP or by COB, Monday, October 5, 2015. If additional detail is available such that generation of narrative summaries would be feasible to address item 2, provide a reasonable timeline for narrative submission. If you have any questions, please contact Colette Jackson, Regulatory Project Manager, at 301-796-1230.

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/s/

COLETTE C JACKSON
09/24/2015

BLA 761033
Reslizumab
Teva Pharmaceuticals

Your submission dated March 30, 2015, to BLA 761033 is currently under review. We have the following comments and/or request for information:

We note that you have conducted a broad standard MedDRA query (SMQ) for "Anaphylactic Reaction" in your integrated safety database. Based on the occurrence of anaphylaxis in your clinical development program, we request further analysis to identify potential additional cases.

1. Of the cases identified via the broad standard MedDRA query (SMQ) for 'Anaphylactic Reaction' in your integrated safety database, identify the subset with onset of reaction within 24 hours of study drug administration. Generate patient narratives for the subset of cases with onset of reaction within 24 hours of study drug administration. Once generated, submit these narratives for review.

   In addition, we request that you assemble an independent committee to adjudicate these subset of cases with onset of reaction within 24 hours to identify cases of anaphylaxis by NIAID/FAAN criteria (Sampson H et al, 2006). For the evaluation of new molecular entities, DPARP has identified anaphylaxis using criterion #1, in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. In addition, any cases reported by investigators or other healthcare professionals as "anaphylaxis" or "anaphylactoid" are accepted as cases of anaphylaxis, even if the case report does not detail more specific signs and symptoms. The adjudication committee should be blinded to treatment and eosinophil count.

2. Resubmit the ISS DDAE database with three additional variables:

   a. minutes from study drug administration to earliest time of onset of the SMQ anaphylactic qualifying adverse event for all patients identified via the broad anaphylactic SMQ
   b. flag variable identifying the subset of patients with onset within 24 hours of study drug administration
   c. study drug received prior to onset (placebo vs. reslizumab and dose)

For number 2 of the information request, we request your reply by COB, Friday, September 11, 2015. For number 1, we request the narratives once generated; the results of the adjudicated review should be submitted ASAP, but no later than COB, October 31, 2015. If you have any questions, please contact Colette Jackson, Regulatory Project Manager, at 301-796-1230.

References:

Sampson HA et al *J Allergy Clin Immunol 2006;117:391-7*

Reference ID: 3815580

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/s/

COLETTE C JACKSON
09/03/2015

PDUFA V Program Mid-Cycle Communication Agenda

BLA 761033 Reslizumab

Teleconference
September 8, 2015
4:00 – 5:00 PM EST

1. **Teva/FDA Review Team 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**

- As communicated in the filing letter, the lack of evidence for a reduction in exacerbations is noted for the following key subgroups: patients 12 to 17 years of age, black patients, and US patients. This remains a review issue.

- Concerns regarding the large number of protocol violations, the timing of protocol amendments relative to enrollment, the misclassification of a stratification variable, and the timing of database finalization relative to unblinding have not been resolved and remain significant review issues.

- An information request will be sent to request data on the neutralizing capacity of the anti-drug antibodies detected in patient samples that confirm positive as well as validation report for the neutralizing antibody assay used to test these samples.

- To date we have communicated two CMC information requests:

    - On August 24, 2015, we requested information on microbial and endotoxin control of reslizumab drug substance and drug product, including process validation and the container closure integrity test for reslizumab drug product.

Reference ID: 3815584

We requested response to this information request prior to September 11, 2015.

- On July 13, 2015, we requested information on process validation of reslizumab drug substance and revision of the facilities listed in the application 356h form. We received response to this information request. The data are currently under review.

1. Major Safety Concerns

- We note the higher rate of anaphylaxis in patients treated with reslizumab compared to those treated with placebo. In an information request dated September 3, 2015, we have requested a more detailed clinical analysis of potential anaphylaxis cases using NIAID/FAAN criteria.

- An information request will be sent to request the development of a sensitive and product-specific IgE antibody assay and analysis of sera samples from patients who developed anaphylaxis. This information is needed because we are concerned that episodes of anaphylaxis may be triggered by anti-drug IgE antibodies in susceptible patients. Although your three confirmed patients were reportedly anti-drug antibody negative, your screening antibody assay has a sensitivity of 22 ng/ml; which is insufficient to detect clinically relevant IgE. Typically a sensitivity below 5 ng/ml is needed in order to detect clinically relevant IgE.

- You provided data on the characterization of relative percentage of neutral glycans for batch 202709 ARS in your BLA submission. (b) (4) An information request will be sent to request characterization data on alpha-gal species in reslizumab throughout development, including batches used in the clinical studies that you intend to use to support your application.

- CPK elevations are noted as a safety signal in your development program. Whether any cases meet the criteria for rhabdomyolysis is under review. An information request will be forthcoming soon requesting additional information for further evaluation of this safety signal.

2. Risk Management Update

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

3. Advisory Committee Meeting Plans

- An Advisory Committee Meeting to discuss this application is currently scheduled for December 9, 2015. Anticipated topics for discussion are outlined under Headings 2 and 3, Significant Review Issues and Major Safety Concerns, respectively.

4. Date and Format for Late-Cycle Meeting

- November 23, 2015; Face to Face meeting.

Drafted by:	Banu Karimi-Shah/ September 1, 2015
Cleared by:	Badrul Chowdhury/September 1, 2015
	Sandy Barnes/September 3, 2015
Finalized by:	Colette Jackson/September 3, 2015

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/s/

COLETTE C JACKSON
09/03/2015

We refer to Reslizumab BLA 761033 submission dated March 30, 2015, which is currently under review. We have the following request for information:

1. With reference to study #P-6378 entitled "*Intravenous Embryo-Fetal Development Study of SCH 557000 in Mice,*" provide justification (e.g., laboratory historical control data from age-matched animals) that the finding of asymmetrical sternebra, which was observed with increased incidence in drug-treated animals versus controls, is not related to reslizumab treatment.

2. With reference to study #DS-2010-020 entitled "*Perinatal/Postnatal Reproduction, Developmental, and Juvenile Toxicity Study of Intravenous Reslizumab in Mice, Including a Postnatal Behavioral/Functional Evaluation,*" provide justification (e.g., laboratory historical control data from age-matched animals) that the finding of decreased sperm motility, which was observed in F1 generation males from treated dams (22% decrease at 10 mg/kg and 26% decrease at 50 mg/kg, versus controls), is not related to reslizumab treatment.

Provide responses to this information request by 5:00 pm, EST on August 27, 2015 by email at Colette.Jackson@FDA.HHS.GOV or facsimile to 301-796-9728. A formal submission to the BLA should be made shortly thereafter. If you have any questions, please contact Colette Jackson, Senior Regulatory Program Manager, at 301-796-1230.

Drafted by: L. Hann/ August 20, 2015

Initialed by: S. Barnes/ August 20, 2015
C. Galvis/ August 19, 2015
M. Wood/ August 19, 2015

Finalized: L. Hann/ August 20, 2015

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/s/

LEILA P HANN
08/20/2015

BLA 761033
Reslizumab

Your submission dated March 30, 2015, to BLA 761033 is currently under review. We have the following comments and/or request(s) for information:

1. Identify the testing platform(s) used to measure eosinophil counts in the reslizumab clinical development program; provide your plan to address the generalizability of the counts to clinical practice when alternate measurement platforms are used with different reference ranges. One approach may be to compare counts obtained on your platform against other measurement platforms with a broad range of reference ranges as well as against manual counts. However, we acknowledge that other approaches to address this concern may be sufficient and/or preferable.

2. Complete the demographics table for:
   - All study subjects
   - For U.S. subjects vs. non-U.S. subjects
   - For study subjects 12 < 18 years old

	Study 3081	**Study 3082**	**Study 3083**	**Study 3084**
Demographics				
Age, mean in years Asthma duration, mean in years Percentage patients never smoked				
Pulmonary function tests				
Pre-bronchodilator FEV_1, mean % predicted Pre-bronchodilator FEV_1/FVC ratio, mean Reversibility, mean % ΔFEV_1 post-SABA Post-bronchodilator FEV1/FVC, mean				
Eosinophil Counts				
Baseline mean blood eosinophil count /μL				
Exacerbation history				
Mean number of exacerbations in previous year				
Percentage patients with ≥2 exacerbations in previous year				
Percentage patients with ≥3 exacerbation in previous year				
Background treatments for asthma (%)				
Moderate-dose inhaled corticosteroids (ICS)				

Reference ID: 3802315

High-dose inhaled corticosteroids (ICS) Non-ICS controller drug Oral corticosteroids (OCS)				

3. While we note the definition of asthma exacerbation that you have utilized in your clinical development program, in preparation for the advisory committee meeting, the Division will present the analysis of exacerbations by severity defined in the following way:
    - Severe: hospitalization or > 24 hour ER stay
    - Moderate: initiation of or increase in systemic corticosteroids
    - Mild: anyone else meeting Teva's original CAE definition not captured in the above categories (increase in ICS, symptoms, decreased lung function, ED visit < 24 hours, unscheduled physician visit)

    Analyze CAE based on severity level as described above for studies 3082 and 3083. Provide the datasets and programs for these analyses.

4. We note the occurrence of anaphylaxis in your clinical development program. Provide a description of how anaphylaxis was captured and analyzed in your development program. A broad query and analysis of additional potential anaphylaxis cases will be required, and a more detailed information request regarding conduct of this analysis will be forthcoming shortly.

5. There were multiple misclassifications of the stratification variable 'asthma exacerbation within the last 12 months' in studies 3081 and 3084. There were also several misclassifications of the stratification variable 'baseline oral corticosteroid use' in studies 3082 and 3083. Provide clarification on patient level data to explain how these discrepancies occurred.

6. For studies 3081, 3082, 3083, and 3084 provide the following:
    - Date the last patient completed their last visit
    - Date of database lock and unblinding
    - Date the statistical analysis plan was finalized
    - For study 3082, provide the rationale for changing the primary endpoint after enrollment was completed.

7. To examine the potential effect of missing data on results from studies 3081, 3082, and 3083, provide tipping point sensitivity analyses. These analyses should employ the same models as your primary analyses, with multiple imputations varying assumptions about average values among the subsets of patients who had missing data. The goal of these tipping point analyses is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. These tipping point analyses should be provided for the following endpoints:

Reference ID: 3802315

- For studies 3082 and 3083 examine clinical asthma exacerbations (CAE) and CAEs by severity as defined in comment 3 above .
- For study 3081, examine change in FEV1 from baseline over 16 weeks.

Provide the datasets and programs for these analyses. The analysis datasets should include columns which clearly indicate whether each observation and the associated baseline measurement was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

8. Conduct subgroup analysis separately for each of studies 3081, 3082, and 3083. Submit datasets and programs for these analyses.
   - For Study 3081, analyze FEV1 by the following subgroups: age, sex, race, geographical region, asthma exacerbation within the last 12 months.
   - For Study 3082 and Study 3083, analyze CAE (all, severe, moderate, mild) and FEV1 improvement by the following subgroups: age, sex, race, geographical region, OCS use at baseline, LABA use at baseline, LTRA use at baseline.

9. Provide details for the disclosable financial arrangements pertinent to criteria #2 (payments such as grants, equipment, retainer or honoraria) regarding the financial disclosure for (b) (6)

10. Provide a rationale for excluding n=15 subjects from the terminated study sites (864 and 909) from the safety analysis datasets in study 3084.

11. We note that analyses for quality of life measures were performed over variable time spans, for example ACQ was measured over 16 weeks whereas AQLQ was measured at 16 weeks. Repeat all of the QOL analyses (responder analysis using the MCID as threshold) using both approaches – at 16 weeks and over 16 weeks for each instrument in studies 3081, 3082, and 3083. These measures typically are done at a time point as the measure itself incorporates recall period. Please explain why these measures were conducted in two different ways, at a time point, and over a time period.

12. It is unclear how data were captured and coded for the asthma exacerbation endpoint, as there appear to be fewer fields in the case report form (CRF) than there are in the protocol definition or the dataset (see table below):

Reference ID: 3802315

Protocol Definition	CRF fields	Dataset Variable
New use of systemic corticosteroids	Have oral corticosteroids been newly prescribed or baseline dose of oral corticosteroids increased?	Use of systemic only corticosteroids
Increase in the use of inhaled, corticosteroid treatment for 3 or more days (for patients already being treated with systemic or inhaled corticosteroids, the dose of corticosteroids will need to be increased 2 or more fold for at least 3 or more days)		Use of systemic or inc in inhaled cs
Unscheduled visit to the physician's office for nebulizer treatment or other urgent treatment to prevent worsening of asthma symptoms	Emergency treatment because of asthma	Unscheduled visit to physician's office
Visit to the emergency department for asthma related treatment		Visit to emergency room
Asthma related hospitalization	A hospitalization because of asthma	Asthma related hospitalization
Decrease in FEV1 by 20% or more from baseline	A decrease in FEV1 by 20% or more	Dec in FEV1 by 20% or more
Decrease in PEFR by 30% or more from baseline on two consecutive days	A decrease in PEFR of 30% or more from baseline on two consecutive days, directly resulting in an increase in ICS or OCS dose based on clinical assessment	Dec in PEFR below 30%
Worsening of symptoms or other clinical signs per physician evaluation of the event		Worsening of symptoms
Source: Study 3082 Protocol p. 55	Source: Study 3082 Sample Case Report Form, Clinical Asthma Exacerbation and Clinical Asthma Exacerbation 2, pgs. 78 and 79	Source: Study 3082 dataset ADCAEA.XPT variable PARAM

Reference ID: 3802315

a. For studies 3082 and 3083, explain how the exacerbation definition as outlined in the protocols was captured in the CRFs, and in turn, how these CRFs were coded into the analysis datasets. Include annotated and sample CRFs and syntax where relevant.

b. Include a copy of provide the location within the BLA submission for the Adjudication Specific Case Report Forms (eCRFs) and provide an explanation as to how these eCRFs were generated.

c. Provide minutes (or location with the BLA submission) from the adjudication committee meetings.

We request your reply by COB, Friday, August 21, 2015. If you have any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Reviewer initiated fax: August 5, 2015
Routing:

Sandy Barnes/ August 5, 2015
Kathleen Donohue/ August 5, 2015
Banu Karimi-Shah/ August 5, 2015
Lan Zeng/ August 5, 2015
David Petullo/ August 5, 2015

Finalized: Colette Jackson/ August 5, 2015

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/s/

COLETTE C JACKSON
08/05/2015

MEMORANDUM of TELECONFERENCE

MEETING DATE: April 21, 2015
TIME: 11:30 am EST
LOCATION: CDER WO 22/Rm 4322
APPLICATION: BLA 761033
DRUG NAME: **Cinqair** (reslizumab) Injection, 100 mg
TYPE OF MEETING: Teleconference

MEETING CHAIR: Lubna Merchant, PharmD
MEETING RECORDER: Nichelle Rashid

FDA ATTENDEES:

Office of Surveillance and Epidemiology
Nichelle Rashid, Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis
Lissa Owens, RPh, Safety Evaluator
Kendra Worthy, PharmD, Team Leader, DMEPA
Lubna Merchant, MS, PharmD, Associate Director, DMEPA

SPONSOR ATTENDEES:

Teva Pharmaceutical, :
Christine Kampf, Associate Director, Regulatory Affairs, Teva
Ken Bonk, Senior Director, Regulatory Affairs, Teva
(b) (4)
Hugh Fosbury, Senior Director, Global Respiratory Marketing, Teva

BACKGROUND:

The applicant initially submitted the proposed name, [redacted] for IND [redacted] on May 2, 2008. DMEPA found the name acceptable.

Subsequently, the applicant submitted the proposed name, Cinqair to BLA 761033 on March 29, 2015; which has an OSE PDUFA date of June 28, 2015.

MEETING OBJECTIVES:

The Division of Medication Error Prevention and Analysis (DMEPA) requested a teleconference to get clarification from the sponsor regarding [redacted]

REGULATORY OPTIONS:

1. Withdraw the proposed name, [redacted]
2. Withdraw the proposed name, Cinqair and submit [redacted] to the BLA for review.

DISCUSSION:

Teva was unaware that the previous owner, Ception Therapeutics, has submitted a request for proprietary name review under IND [redacted] Teva had no clarifying questions regarding the two names [redacted]

Teva will confirm their regulatory options by closed of business, Wednesday, April 22, 2015.

ADDENDUM:

On April 22, 2015, Teva Pharm confirmed that they would withdraw the request for the proprietary name review, [redacted] under IND [redacted] and would like DMEPA to continue the review on the proposed proprietary name, Cinqair submitted under BLA 761033.

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/s/

NICHELLE E RASHID
06/25/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761033

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
Frazer, PA 19460

ATTENTION: Christine M. Kampf
Associate Director, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Reslizumab, 10 mg/mL.

We also refer to your March 29, 2015, correspondence, received March 30, 2015, requesting review of your proposed proprietary name, Cinqair.

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

If any of the proposed product characteristics as stated in your March 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. 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/

TODD D BRIDGES
06/25/2015

Executive CAC
Date of Meeting: June 16, 2015

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Abby Jacobs, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, ONDIO, Member
Todd Bourcier, PhD, DMEP, Alternate Member
Marcie Wood, PhD, DPARP, Pharm Tox Supervisor
Carol M. Galvis, PhD, DPARP, Presenting Reviewer

Author of Minutes: Carol M. Galvis, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

BLA # 761,033
Drug Name: Reslizumab
Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Teva Branded Pharmaceutical Products conducted a 26-week study in Tg.rasH2 mice to assess the carcinogenic potential of reslizumab. The study protocol was discussed with the Executive CAC in a meeting held on July 10, 2012. The study design and reslizumab doses were considered adequate by the Committee (refer to meeting minutes dated July 11, 2012 under IND 101,399). The sponsor also provided data demonstrating that the transgenic mice were pharmacologically responsive.

Reslizumab was negative in an in vitro bacterial mutagenicity (Ames) assay and an in vitro chromosomal aberration assay.

Tg.rasH2 Mouse Carcinogenicity Study
In the 26-week carcinogenicity study (study #DS-2012-005), Tg.rasH2 mice (25/sex/group) received 0 (vehicle control: 70 mg/mL sucrose, 2.45 mg/mL sodium acetate trihydrate, and 0.12 mg/mL glacial acetic acid), 100, 250, or 516 mg/kg reslizumab intravenously once every two weeks. In addition, a group of 25 mice/sex received 75 mg/kg N-methyl-N-nitrosourea (MNU) intraperitoneally as a positive control. No statistically significant neoplastic findings were observed in male or female mice treated with reslizumab. Reslizumab affected survival in females (statistically significant increase in mortality at the 516 mg/kg dose) but not in males. Toxicokinetics were not conducted in the study.

Executive CAC Recommendations and Conclusions

Tg.rasH2 mouse:

- The Committee concurred that the study doses were acceptable, noting prior ECAC concurrence with the doses.
- The Committee concurred that there were no drug-related neoplasms.

Karen Davis Bruno, PhD
Chair, Executive CAC

cc:\
/ Division File, DPARP
/M Wood, DPARP
/C Galvis, DPARP
/C Jackson, DPARP
/A Seifried, OND IO

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/s/

ADELE S SEIFRIED
06/19/2015

KAREN L DAVIS BRUNO
06/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Reslizumab.

We also refer to your amendments dated April 13, and 30, 2015 and to our June 11, 2015, Filing Communication – Filing review issues identified letter which contained the incorrect user fee goal date.

This replacement letter incorporates the correction of the error.

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 March 30, 2016. 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 December 16, 2015. In

addition, the planned date for our internal mid-cycle review meeting is August 28, 2015. We are 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:

1. The lack of evidence for a reduction in exacerbations is noted for key subgroups, including patients 12 to 17 years of age, black patients, and US patients, and will be a review issue.

2. We note the lack of data supporting your recommendations for handling parasitic disease. This issue may require a Post-Marketing Requirement (PMR).

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.

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* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 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.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)". We note that a pharmacologic class has not been established at this time.

2. In the Table of Contents, the statement "**FULL PRESCRIBING INFORMATION: CONTENTS**" should all be on one line.

3. The Table of Contents should be properly aligned.

4. The horizontal line between the Table of Contents and the Full Prescribing Information should be placed directly under the Table of Contents.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 1, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

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 (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), 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 deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

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/

BADRUL A CHOWDHURY
06/11/2015

July 28, 2015

The attached (COR-BLAFILE-04 Filing Review Issues Identified) letter contained the incorrect user fee goal date.

The communication function of this letter has been changed to Advice. The replacement letter was entered on July 28, 2015, and backdated to June 11, 2015, to maintain the correct goal data, per the original filing letter's date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Reslizumab.

We also refer to your amendments dated April 13, and 30, 2015.

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 March 28, 2016. 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 December 16, 2015. In addition, the planned date for our internal mid-cycle review meeting is August 28, 2015. We are currently planning to hold an advisory committee meeting to discuss this application.

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Food and Drug Administration
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Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

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/

BADRUL A CHOWDHURY
06/11/2015

BLA 761033
Reslizumab

We are currently reviewing your BLA submission dated March 29, 2015, and we have the following requests for information.

Submit the following datasets and modeling scripts for the population pharmacokinetic/pharmacodynamic analysis in report CP-15-001:

1. Provide all datasets used for model development. Submit the datasets as SAS transport files (*.xpt). Provide a description of each data item in a Define.pdf file. Flag and maintain any data point and/or subjects that have been excluded from the analysis in the datasets.

2. Provide model codes. Provide output listings for all major model building steps, e.g., base structural model, full model, and final model. Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

If you have submitted this information, please provide their location in the submission.

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

Drafted: Colette Jackson/April 28, 2015

Initialed:

Sandy Barnes/ April 28, 2015
Yunzhao Ren/ April 27, 2015
Yaning Wang/ April 27, 2015

Finalized: Colette Jackson/April 28, 2015

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/s/

COLETTE C JACKSON
04/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

BLA ACKNOWLEDGMENT

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

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: Reslizumab

Date of Application: March 29, 2015

Date of Receipt: March 30, 3015

Our Reference Number: BLA 761033

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 May 29, 2015,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. 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/

COLETTE C JACKSON
04/15/2015

Your BLA 761033 submission for reslizumab has been received, and we have the following request for information:

The clinsite.xpt file (CDER's Clinical Site Selection Tool) contains a number of missing and incorrectly formatted variables that prevents us from being able to use the dataset(s). Although the file is labeled clinsite.xpt in the submission backbone, when the file is opened, it is actually titled "CS_BINED" – was the wrong file submitted in the application?

Submit a revised clinsite.xpt file correcting or explaining the following items:

1. For Study 3085, variable "DBARM" - explain how/why subjects are assigned to Placebo vs Reslizumab, as well as the difference between the two groups of subjects at each site. It is our understanding that all subjects received active drug.
2. Correct Variable label "MININIT" to "MINITIAL".
3. Variable "Lastname" has 574 blank entries; enter the Principal Investigator's last name for each site (most recent PI as listed on FDA Form 1572 or investigator agreement should be used).
4. Variable "STREET" has 739 blank entries; enter street address for each site.
5. Variable "CITY" has 566 blank entries; enter city for each site.
6. Numerous invalid characters are present in the investigators name, contact, and address fields (" "); remove invalid characters from the dataset(s).

Submit the requested information as an official response to the BLA no later than close of business (COB) Wednesday, April 15, 2015. If you have any questions, please contact Ms. Colette Jackson at 301-796-1230.

Drafted by: AOrencia/ 4.1.2015
cford/ 4.1.2015

Initialed by: SBarnes/ 4.1.2015

Finalized: cford/ 4.1.2015

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/s/

CHRISTINE H CHUNG
04/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101399

MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Reslizumab (CEP 38072).

We also refer to the teleconference meeting between representatives of your firm and the FDA on January 15, 2015. The purpose of the meeting was to discuss your planned BLA submission.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	January 15, 2015, at 2:30 PM EST
Meeting Location:	via teleconference
Application Number:	IND 101399
Product Name:	Reslizumab (CEP 38072)
Indication:	Asthma
Sponsor/Applicant Name:	Teva Pharmaceuticals
Meeting Chair:	Lydia Gilbert-McClain, M.D., Deputy Director, DPARP
Meeting Recorder:	Colette Jackson

FDA ATTENDEES
Curtis Rosebraugh, M.D., Director, Office of Drug Evaluation II, OND
Lydia Gilbert-McClain, M.D., Deputy Division Director, DPARP
Kathleen Donohue, M.D., Clinical Reviewer, DPARP
Ping Ji, Ph.D., Clinical Pharmacology Reviewer
Satjit Brar, Ph.D., Clinical Pharmacology Team Leader
Yu Wang, Ph.D., Statistical Reviewer
David Petullo, Ph.D., Acting Statistical Team Leader
Cecilia Tami, Ph.D., Product Quality Team Leader
Tracey Denison, Ph.D., Product Quality Reviewer
Ramesh Potla, Ph.D., Product Quality Reviewer
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(b) (4)

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Matthew Seavey, Manager, Pharmacology Project Leader

1.0 BACKGROUND

Teva Pharmaceuticals sent in a Type B meeting request dated October 17, 2014, to discuss the planned BLA submission for reslizumab. The Division granted the meeting on November 7, 2014. Teva Pharmaceutical provided their briefing materials on November 13, 2014. The FDA sent Preliminary Comments to Teva via email on January 13, 2015. On January 14, 2015, Teva outlined their discussion points via email and provided a response document specifically for discussion of Question 9.5. This response document was officially submitted to the IND on February 5, 2015, and is attached to these meeting minutes in Section 6.0. Teva's questions and the FDA responses are 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. Teva Pharmaceuticals' questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2. DISCUSSION

REGULATORY

9.1. Contents of the Biologics License Application (BLA)
The proposed Table of Contents of our BLA for reslizumab, outlining the high-level content of a complete application, is provided in this meeting background package. Additionally, detailed shell documents for the ISS and ISE are also provided. Further, Question 9.14 provides a detailed summary of the stability data to be included in the original submission as well as in a minor amendment, within 30 days of the original BLA submission, containing additional stability data.

Does the Division agree with the overall contents of the planned BLA?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

9.2. Priority Review

Teva plans to request Priority Review designation for this BLA on the basis that there are currently no treatments available for moderate to severe asthmatics with elevated blood eosinophils who are at risk for exacerbations despite standard of care treatment for this population. This is a serious condition and reslizumab has demonstrated a significant improvement on top of standard of care in this population.
Does the Agency have any advice or recommendations for our planned request for Priority Review?

FDA Response:
The determination of whether the submission meets criteria for priority review designation as outlined in the draft Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (June 2013) will be made at the time of BLA submission. However, at this time your proposal does not appear to qualify for priority review designation, as this subgroup of patients could be treated with steroids or other available therapies.

Discussion:
There was no discussion held for this response.

9.3. Potential for Advisory Committee
Reslizumab is a new molecular entity and potentially a first in class anti-IL-5 monoclonal antibody intended for the treatment of a specific phenotype of moderate to severe asthma associated with elevated blood eosinophils.
Does the Agency anticipate that this BLA would be presented to an Advisory Committee prior to an action being taken?

FDA Response:
The determination of whether this BLA would be presented to an Advisory Committee will be made at the time of the BLA submission. It would be premature to comment at this time.

Discussion:
There was no discussion held for this response.

9.4. REMS
Based on the current perceived risk benefit profile seen with reslizumab to date, Teva is anticipating that a Risk Evaluation and Mitigation Strategy (REMS) would not be required to ensure the benefits of treatment with reslizumab continue to outweigh the risks once it is commercially available. Consistent with other recently approved biologics, Teva does plan to develop and submit a medication guide as a component of the Full Prescribing Information to communicate the identified risks and appropriate use of reslizumab in consumer friendly language.
Does the Agency agree with this approach?

FDA Response:
At this time, we do not have sufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not

believe that a REMS or a medication guide will be necessary. We will make a final determination for the need for a REMS and a medication guide during the review of your application.

Discussion:
There was no discussion held for this response.

CLINICAL

9.5. Handling of Reslizumab Serum Concentration Data for the Population Pharmacokinetic Analyses
In the reslizumab clinical development program, serum samples were analyzed for reslizumab concentration. Detectable values were present in a subset (approximately 25%) of the baseline and placebo samples due to presumed sample matrix effects. As a result, Teva proposes to establish a pre-specified operational cutoff for inclusion of data in the population PK analyses. This cutoff has been selected based on review of the concentration data and represents a small percentage of Cmax.
Does the agency concur with the use of a pre-specified cutoff for data handling in the population PK analyses?

FDA Response:
We do not agree. You concluded from the bioanalytical investigation report that the baseline and placebo quantifiable values do not have any significant impact on reslizumab PK assessment. Therefore, regardless of pre-specified cutoff, the PK analysis should not be impacted for either population PK analysis or the PK analysis for individual studies. However, you did not provide a rationale on why the results may be biased if no cut-off is used in the population PK analysis. You should provide justification for the use of the cut-off and conduct the PK analysis, for the popPK study, with and without your specified cut-off.

Discussion:
Teva referred to their response document which stated that if small, non-clinically meaningful differences in steady-state PK parameter estimates are observed between the original analysis (with the cut-off) and the repeat analysis (without the cut-off), the full analyses (including PK/PD) would not be repeated. Teva asked the FDA if this is acceptable. The FDA asked Teva what plans they have if the initial analysis without cut-off shows different results versus those initially with a cut-off. Teva stated that if differences are observed between the 2 analyses, they will do a full analysis with and without cutoffs. The FDA stated that this is acceptable. The analysis dataset with and without cut-off should be submitted in the BLA application.

9.6. Presentation and Analysis of Anti-Drug Antibody Data
In the BLA submission, the ADA data set will cover the BREATH program without study 3085. ADA data from the ongoing Study 3085 will be presented in the 120-day safety update submission along with an Integrated Immunogenicity Report. For each of completed studies, a bioanalytical report will be provided in the BLA to detail multiple-tiered analysis results, including screening, confirmation, and titer results. Teva's approach for reporting ADA data is provided.

Does the Agency agree or have any advice on the ADA assessment and approach for reporting ADA data in the BLA?

FDA Response:
The proposed ADA data analysis appears reasonable but the final determination of the suitability of the approach will be a review issue. Assay validation studies along with information on how you established critical assay parameters that were not validated should be provided in module 5.3.4.1 Reports of Bioanalytical Methods for Human Use. Circulating levels of IL-5 or reslizumab may be high enough to interfere with the detection of ADA. Your ADA assay validation package should describe how you managed the potential for interference by endogenous IL-5 and reslizumab.

Discussion:
There was no discussion held for this response.

9.7. Submission of Open-Label Extension Study Data
Study conduct is ongoing for Study 3085, the open-label, long-term safety study for reslizumab. A cut-off date of September 1, 2014 will be used for inclusion of data in the ISS and an interim CSR. PK data obtained prior to the cutoff date are planned to be included in the original BLA. However, ADA data will not be included in the original BLA submission, but will be provided in the 120-day safety update. The 120-day safety update will include the final clinical study report for study 3085 as well as any required new case report forms (CRFs) and corresponding patient narratives as outlined in the Company position.
Does the Agency agree with this approach?

FDA Response:
Your approach may be reasonable. Ultimately, your BLA should be complete at the time of filing, with all the information necessary to complete our review. Completeness of the application will be assessed at the time of filing, not based on what may be submitted at the 120-day safety update.

Discussion:
There was no discussion held for this response.

9.8. Integrated Summaries of Safety and Efficacy
Consistent with section V, example A of the Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, Teva proposes to provide an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) that follows the structure for Module 2.7.3, Summary of Clinical Efficacy and Module 2.7.4, Summary of Clinical Safety with additional tables included as appendices. Shells and Statistical Analysis Plans (SAPs) for the ISE and ISS are provided within this submission. These supporting ISS and ISE documents will reside within Module 5.
Does the Division agree?

FDA Response:
We agree. Include the syntax file used to generate the tables in the Integrated Summary of Safety.

Discussion:
Teva asked the FDA to clarify "syntax file" noted in the Agency response. The FDA stated that it refers to the SAS programs used for derived datasets and summaries in the ISS.

9.9. Submission of Datasets
The planned submission format and datasets to be included in the BLA will follow the Study Data Specifications guideline published by FDA in July 2012 (version 2.0). The proposed datasets to be included in the BLA as well as details regarding format are detailed in the Company Position.
Does the Division agree or have any advice on the plan?

FDA Response:
Your approach is acceptable. Also include all programs, including macros, used to generate your derived datasets and analyses.

Discussion:
Teva referred to the following clarification statement outlined in their January 14, 2015, email:

Regarding the comment to "include all programs, including macros, used to generate your derived datasets and analyses" can FDA confirm agreement with the following:

a. *Teva will provide these programs only for studies 3081, 3082, 3083, 3084 and 3085, the ISS and the ISE. The conversion programs for other studies will not be provided.*
b. *The programs will be submitted as one zip file containing 3 folders: programs, macros, DOCS (titles.xls and readme.doc)*
c. *Programs for key efficacy analyses will be submitted as executable programs which will enable execution on other platforms*

The FDA agreed with this approach.

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9.10. Submission of Bioresearch Monitoring Data
Teva will provide the following site level data in the BLA in accordance with the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning. This data will be provided following the Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning (version 1.2). The proposed study data to be included in the BLA as well as details is provided in the Company Position.
Does the Division agree?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

9.11. Submission of Case Report Forms and Patient Narratives
In accordance with 21 CFR 314.50 and Industry standard for reporting, Teva will provide CRFs for any patient who:

- ***experienced serious adverse events during a clinical study;***
- ***discontinued from a clinical study due to adverse events, whether believed to be drug related or not, including subjects receiving placebo;***
- ***died during a clinical study***

All CRFs will be provided as Portable Document Format (PDF) files, organized by study, site and patient.

In addition, patient narratives will be prepared for any patient who falls into any of the above listed categories. These narratives will accompany the individual CSRs for the study in which the event occurred.
Does the Division agree?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

Additional Clinical Comment:
We note that there have been no reports of helminthic parasitic infections for the completed reslizumab studies thus far. However, we reiterate our comment from the End-of-Phase 2 (EOP2) meeting that your clinical program will need to address the risk of parasitic infections with reslizumab treatment. The adequacy of the data for evaluating the risk of parasitic infection will be a review issue, with potential implications for labeling and post-marketing requirements.

Discussion:
Teva asked the FDA to clarify the concern for helminthic parasitic infections and noted that there have been no reports of such infections in their reslizumab trials. The FDA stated that, as a follow up to our comment relayed at the August 18, 2010, End-of-Phase 2 meeting, there is a continued safety concern of parasitic infections given the proposed mechanism of action of reslizumab and what is known regarding the biological activity of eosinophils. The FDA suggested Teva look at the Xolair label in which a dedicated study was conducted and noted that Teva should plan to address this issue when they submit their BLA.

STATISTICS

9.12. Integrated Summary of Safety

a. Teva proposes to perform integrated analyses of safety data from studies evaluating patients with asthma (Cohorts 1-5) and all exposed subjects (Cohort

6), irrespective of disease state. Cohort 6 was identified primarily for detection of rare events, following approval of the ISS SAP. These cohorts are described in the company position below.
Does the Division agree with the cohorts that will be utilized in the proposed integrated safety analyses?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

b. Teva proposes that the ISS statistical analysis plan (SAP), with the corresponding ISS shell document, and proposed tables sufficiently address the requirements to evaluate the safety of reslizumab.
Does the Division agree?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

c. Teva proposes to utilize adverse events for Cohort 3 (e.g., all controlled asthma studies utilizing the 3.0 mg/kg dose and q 4 week regimen up to 52 weeks) as the primary means of evaluating adverse events as reflected in the structure of the ISS shell. Teva also proposes that identification of Adverse Drug Reactions will be based on evaluation of both placebo-controlled cohorts (e.g., occur at a frequency ≥ 1% more on reslizumab versus placebo) and on Cohort 6 (all reslizumab studies) along with the application of medical judgment. Additional detail is provided in section 9.5 of the ISS shell.
Does the Division agree?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

9.13. Integrated Summary of Efficacy (ISE)
In the Integrated Summary of Efficacy (ISE), Teva proposes to present individual efficacy study data side by side with integrated analyses where study designs are highly similar:

a. Teva proposes that the ISE SAP, with the corresponding ISE shell document, sufficiently address the requirements to evaluate the efficacy of reslizumab.
Does the Division agree?

FDA Response:
We agree.

Discussion:
There was no discussion held for this response.

b. Additionally, Teva intends to pool CAE data across the 52 week studies as prospectively described in the ISE SAP. We believe that this will provide information relevant for evaluation of rare events (e.g., hospitalizations and emergency room visits) in the composite CAE definition.
Does the Division agree with this approach?

FDA Response:
We agree.

Additional Statistical Comments:
Your BLA should contain a tipping point sensitivity analyses for all key efficacy endpoints in your confirmatory studies.

Discussion:
There was no discussion held for this response.

CMC

9.14. Submission of Stability Data
The BLA submission will contain 36 months of drug product (DP) and drug substance (DS) stability data from the primary stability lots. During the BLA review cycle, Teva would like to submit supportive stability data from these lots tested with the new analytical methods, (b) (4) as a minor amendment to the application. Bridging of stability results for both old and new methods, i.e., (b) (4) was discussed at the June 11, 2014, Type C meeting. The Agency requested that both old and new methods be run concurrently for several time points.
Does the Agency agree that updated stability data can be submitted as a minor amendment during the review of the BLA application, and thus will not extend the review clock?

FDA Response:
We agree that minor stability updates do not usually extend the review clock, however, such a determination will be a review issue upon receipt of supportive stability data.

Discussion:
There was no discussion held for this response.

Product Quality Microbiology Comments:
Please refer to the minutes from the CMC meeting held on June 11, 2014, in which you were provided additional guidance on the BLA content from a Product Quality Microbiology perspective. As stated in the minutes, (b) (4)

(b) (4)

lternative approaches will need to be taken to assess the pyrogen content of finished drug product.

Discussion:
Teva noted that they have performed a study to evaluate the effect of hold time on endotoxin recover and will include this information in the BLA. Teva asked the FDA to clarify which eCTD section of the BLA would this information be placed. The FDA advised Teva to place it in section P.5, Control of Drug Product and Validation of Method, P.5.3. If this is effect is also related to the drug substance, the information would be placed in S.4. The FDA also noted that if low endotoxin recovery effects are seen, a pathfoward will have to be found to ensure non-pyrogenicity of the finished drug product.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) 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.

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. 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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.

6.0 ATTACHMENTS AND HANDOUTS

Teva's response document sent via email on January 14, 2015, and submitted officially to the IND on February 5, 2015.

Teva Response to Agency Feedback on Question 9.5, Handling of Serum Concentration Data for the Population PK analyses

Teva appreciates the agency's feedback. As noted, the bioanalytical method used is robust and provides reliable reslizumab concentration measurements. Also as noted, the potential for bias was cited as justification for the use of the operational cutoff. Depending upon the number of affected samples and the time at which they were collected relative to dosing, those samples with presumed matrix effect could possibly impact estimates of clearance, resulting in higher exposure estimates for the subjects affected. If these patients happen to have extreme values of a particular covariate or a high frequency of use of particular concomitant medication (or other covariate), it was considered possible that the covariate analysis findings could be affected.

At the time the briefing package was submitted, activities related to building the population PK dataset were underway but not yet complete. As such, although it was known that a limited amount of the data (< 2%) would likely be removed as a result of applying an operational cutoff, the exact amount was unknown at that time. The population PK datasets are now complete and it is confirmed that only approximately 1.5% of the data were excluded. In light of this, the potential for bias in the model either with or without these samples is considered unlikely.

The majority of population PK and PK/PD analyses are now complete (with the operational cutoff applied). Therefore, Teva proposes to repeat key population PK analysis steps (eg, base structural model, relevant covariate analysis steps, final model, etc.) without the cut-off. The covariate analysis steps to be repeated would be selected based upon review of the affected data. Assuming only small, non-clinically meaningful differences in steady-state PK parameter estimates are observed between the original analysis (with the cutoff) and the repeat analysis (without the cutoff), the full analyses (including PK/PD) would not be repeated.

Does the agency agree that this approach is acceptable?

Reference ID: 3702988

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/s/

COLETTE C JACKSON
02/15/2015

Executive CAC
Date of Meeting: July 10, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Molly E. Shea, Ph.D., DPARP Presenting Reviewer and Supervisor

Also present (b) (4)

Author of Draft: Molly E Shea, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the carcinogenicity bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND # 101,399
Drug Name: Reslizumab
Sponsor: Teva Pharmaceuticals, Inc.

Background:

Teva is developing Reslizumab, a humanized anti-human IL-5 monoclonal antibody, for the treatment of moderate to severe eosinophilic asthma in adolescents and adults (12 years of age and older) whose symptoms are not well controlled with inhaled corticosteroids. (b) (4)

Reslizumab is of the IgG4 kappa isotype that contains the complementarity determining regions of the original rat anti-human antibody (39D10) grafted onto a human framework. In vitro binding and bioassays have demonstrated that reslizumab binds to IL-5 of humans, CD-1 mice, rabbits, guinea pigs, and monkeys. In vivo, the biological activity of reslizumab has been measured in monkeys, rabbits, guinea pigs, and mice using antigen- or human IL-5-induced bronchoprovocation as methods to induce pulmonary eosinophilia and airway hyper-responsiveness.

Tg.rasH2 Mouse Carcinogenicity Study Protocol and Dose Selection:
Teva submitted a special protocol assessment for a proposed 26-week transgenic CByB6F1-Tg(HRAS)2jic mouse study to evaluate reslizumab's potential to induce carcinogenesis. In

support of the proposed 26-week bioassay, a 4-week dose-range-finding intravenous toxicity and toxicokinetic study conducted in 001178-W (Wild type) mice (study number DS-2011-017) was completed at (b) (4) Mice were treated with 0 (vehicle), 250, and 500 mg/kg/dose intravenously on Days 1, 15 and 29 (3 doses total). [A twice-monthly (every 14 days) dosing regimen was instituted for this study based on the calculated half-life of reslizumab in mice (range from approximately 8 to 14 days).] There were no drug-related toxicities observed for all parameters assessed. A maximum tolerated dose was not achieved. The sponsor indicated that the maximum feasible dose was administered to mice (500 mg/kg/dose) based on the clinical concentration of the drug and a maximum dose volume of 5 ml/kg (bolus) based on Diehl *et al.,* 2001[1]. Due to high-concentration of drug present, the ADA assessment was not definitive for ADA presence. The sponsor has not provided support (binding and bioassay) that use of the wild type or transgenic animal species is appropriate in which to assess its toxicity or carcinogenicity. Further, due to the absence of a toxicological or pharmacological observation in this study, it cannot be confirmed that this mouse strain is relevant. If the sponsor can demonstrate that this mouse strain is relevant, then the use of this mouse strain for a carcinogenicity bioassay would be acceptable. For the 4-week dose-ranging study, the NOAEL was identified as 500 mg/kg/dose which is associated with an $AUC_{0\text{-}168\ h}$ of 1326 mg*h/mL for females and 1519 mg*h/mL for males.

The sponsor based their proposed maximum dose on a maximum feasible dose and based on the argument that the high-dose provides an approximate 25-fold AUC ratio (mouse: human). The expected exposure ratios (mouse:human) for the proposed LD (100), MD (250), and HD (500 mg/kg) are approximately 7-, 18-, and 24-fold, respectively, for the maximum proposed clinical dose of 3 mg/kg/dose.

Executive CAC Recommendations and Conclusions:

- The Committee concurred with the proposed doses of 0, 100, 250 and 500 mg/kg once every two weeks, by IV administration, based on this being the maximum feasible dose.
- For transgenic mouse studies, histopathological examination is performed in all dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DPARP
/MShea, DPARP
/CJackson/PM, DPARP
/ASeifried, OND IO

[1] Diehl et al. *A good practice guide to the administration of substances and removal of blood, including routes and volumes.* Journal of Applied Tox. 21. 15-23 (2001)

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/s/

DAVID JACOBSON KRAM
07/11/2012

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	August 18, 2010 1:30 PM to 3 PM
Meeting Location:	Food and Drug Administration 10903 New Hampshire Avenue Building 22, Conference Room 1417 Silver Spring, Maryland 20993
Application Number:	IND 101,399
Product Name:	Reslizumab
Received Briefing Package	July 21, 2010
Sponsor Name:	Cephalon
Meeting Requestor:	Sheila Mathias Director, Regulatory Affairs
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D. Division Director
Meeting Recorder:	Colette Jackson Senior Regulatory Health Project Manager

Meeting Attendees:

FDA Attendees

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

Badrul A. Chowdhury, M.D., Ph.D., Director

Susan Limb, M.D., Clinical Team Leader

Jennifer Pippins, M.D., Clinical Reviewer

Molly Topper, Ph.D., Pharmacology/Toxicology Supervisor

Timothy Robison, Ph.D., Pharmacology/Toxicology Reviewer

Colette Jackson, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology

Division of Clinical Pharmacology 2

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader

Ping Ji, Ph.D., Clinical Pharmacology Reviewer

Office of Biometrics

Robert Abugov, Ph.D., Statistical Reviewer

Ruth Davi, Ph.D., Acting Statistical Team Leder

Sponsor Attendees

Cephalon Inc.

Jonca Bull, M.D., US Drug Regulatory Affairs, Liaison Office

Steven (CK) Chang, PhD., Director, Biometrics

Fang Xie, PhD, Director, Biostatistics

Mona Darwish,PhD., Sr. Director and Group Leader, Clinical Pharmacology

George McCormick, PhD., Vice President, Drug Safety and Disposition

James Ottinger, RPh, Vice President, Worldwide Regulatory Affairs

(b) (4), Consultant, Physician, Clinical Research

Srdjan Stankovic, MD, MDSPH, Sr Vice President Worldwide Clinical Research

Sheila Mathias, PhD, Director Regulatory Affairs

Jack Lawler, Director Clinical Operations

(b) (4) Consultant, Physician, Clinical Research

Lesley Russell, EVP Worldwide Medical and Regulatory Operations

1.0 BACKGROUND

Cephalon, Inc. submitted a Type B meeting request dated April 29, 2010, to discuss the Phase 3 development program for Reslizumab. Cephalon's briefing package was submitted on July 20, 2010. Upon review of the briefing package, the Division responded to Cephalon's questions via fax dated August 13, 2010. The content of the fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response under Section 2.0, including any changes in our original position. Cephalon's questions are in ***bold italics***; FDA's response is in *italics*; discussion is in normal font.

2.0 DISCUSSION

Introductory Comments:

The Division has several concerns regarding your clinical development program:

1. *The proposed indication for the treatment of eosinophilic asthma is novel; your program identifies a new clinical phenotype not recognized in current clinical literature. It is unclear how clinicians will be able to identify appropriate patients for reslizumab treatment, since sputum induction for eosinophilia is not part of routine clinical practice and remains an investigational procedure. Co-development of an appropriate diagnostic test will be required for testing in clinical trials, and to guide safe and effective use of your product, if it is to be approved.*

Discussion:

Cephalon noted that literature referring to eosinophilic asthma was provided in the briefing package and asked why this phenotype is not recognized by the Agency. The Agency stated that the phenotype proposed is investigational and not generally recognized in clinical practice. It is unclear how clinicians will be able to identify the appropriate patient population for the proposed product. Cephalon responded by stating that sputum induction (for the evaluation of eosinophils) is a recognized diagnostic procedure. The Agency stated that sputum induction is not widely incorporated into clinical practice, is not standardized, and lacks defined criteria for interpretation.

The Agency stated that Cephalon will need to clearly define the entity of eosinophilic asthma, and develop a reliable diagnostic tool to identify the phenotype that can be made widely available. The diagnostic tool will likely have to undergo formal evaluation and receive approval from the Center for Devices and Radiologic Health.

2. *Reslizumab should be evaluated in both eosinophilic and non-eosinophilic asthma (once the entity is clearly defined) so that the development program can provide sufficient information to support the claim that reslizumab does not have efficacy in non-eosinophilic asthma. Such information may be included in labeling in order to inform health care providers and ensure appropriate use of the drug.*

Discussion:

Cephalon asked the Agency why there is a need to evaluate reslizumab in patients with non-eosinophilic asthma, given that the product is being proposed only for eosinophilic asthma. Cephalon cited existing evidence that it lacks efficacy for the non-eosinophilic asthma phenotype. The Agency replied that labeling must provide sufficient information to guide clinicians regarding the appropriate use of such a product, i.e., the label would include specific information regarding the lack of efficacy in non-eosinophilic asthma in

order to avoid treating patients who are known to be unlikely to benefit. This information must be supported by data. Reasonable evidence must be provided to allow clinicians to conclude that reslizumab lacks efficacy for the non-eosinophilic phenotype.

3. *Asthma therapeutics are usually developed for the entire spectrum of disease; however, reslizumab is proposed only for patients with moderate to severe asthma. Provide a rationale in the application justifying this restriction based on the benefit-risk profile of the proposed product.*

Discussion:

Cephalon noted that Reslizumab is being developed as adjunctive therapy and therefore use in patients with mild asthma is not anticipated. Cephalon asked the Agency why there is a need to evaluate the drug in the full range of asthma if it will only be used in moderate to severe asthma. The Agency replied that how reslizumab will fit into the standard of care for asthma has yet to be determined; therefore, the Agency does not assume at this time that its use will be limited to adjunctive therapy. Furthermore, asthma is a disease characterized by fluctuation; with treatment, a patient with severe asthma may become a patient with mild disease. Without clinical trials evaluating the product across the entire disease spectrum, it is unclear how to address in the label the question of whether to continue or discontinue treatment as the disease state fluctuates. The Agency suggested Cephalon refer to the product labels of inhaled corticosteroids for guidance. If Cephalon chooses to not address the full spectrum of asthma, adequate justification (e.g. safety concerns) must be provided. Reasons related to convenience would not be considered as adequate justification.

4. *The adequacy of dose exploration in the clinical program will be a review issue. We note that trial Res-5-0010 evaluated only the 3.0 mg/kg dose and the proposed Phase 3 trials do not include further dose exploration. We recommend that you conduct further dose-ranging based on a clinical endpoint in the population of interest. Inclusion of more than one dose level in the pivotal Phase 3 efficacy trials may be informative.*

Discussion:

Cephalon acknowledged the Agency's comment and expressed their intent to proceed with the evaluation of a single dose level. The Agency replied that while the choice is at Cephalon's discretion, it is also at their risk. The Agency's view is that dosing has not been fully explored, and question remains whether lower doses may still be effective.. The Agency also added that dose selection should be evaluated with a clinically meaningful endpoint.

Clinical Questions:

1. Does the Agency concur in principle that the 3 studies would be adequate to support BLA approval for the proposed indication?

FDA Response:

No, we do not agree. Refer to the Introductory Comment. Also, replicated trials are required to support a specific asthma exacerbation claim. In general, the adequacy of the data to support approval will be a review issue.

Discussion:

Cephalon asked why there is a need for replicated trials. Cephalon referred to situations with other FDA divisions when only a single trial was necessary. The Agency replied that it cannot comment on decisions regarding products for other diseases, however, with regards to asthma exacerbations, replication of findings is needed.

Cephalon proposed to modify their clinical program to include exacerbations as a key secondary endpoint and asked whether labeling claims regarding exacerbations could be given. The Agency stated that to support labeling claims, the exacerbations endpoint should be treated as a primary endpoint. For example, the analysis of this endpoint should be defined in the protocol and should appropriately account for multiple endpoints. The Agency would critique this endpoint as if it were a primary endpoint.

2. Does the Agency concur that the study population selected for the 3 studies is adequate to support BLA approval for the proposed indication?

FDA Response:

See our Introductory Comment. In addition, we note the plan to stratify patients according to the presence or absence of nasal polyps. The protocol should fully specify the method used to identify polyps, and standard criteria should be employed across centers.

3. (b) (4) ***is proposed as the primary efficacy measure for the pulmonary function studies. Does the Agency concur with the selection of this measure and the overall design of these studies to support the proposed indication?***

FDA Response:

We prefer that you use the absolute forced expiratory volume in 1 second (FEV1), (b) (4) . Absolute FEV1 is the typical efficacy measure of lung function used in other asthma development programs covering the same proposed age range of 12 years and older. Whichever spirometric parameter is selected, the demonstrated treatment difference must be clinically relevant to support a lung function claim. Specify how spirometry will be assessed (e.g. trough vs. peak values) in the protocol.

The protocol synopses do not state whether inhaled corticosteroids will be permitted during the screening and treatment periods. Concomitant use of inhaled corticosteroids is likely to impact patient screening and efficacy. Based on the information provided, we cannot ascertain whether this issue has been taken into account in the proposed trial designs and sample size calculations.

Discussion:

Cephalon stated that they will use FEV1 as suggested by the Agency. Cephalon also noted that the inclusion criteria specify that patients will be on inhaled corticosteroids.

4. Change from baseline in the Asthma Control Questionnaire (ACQ) score will be pre-specified as a key secondary variable for the pulmonary function studies. Does the Agency concur with the selection of this measure to support the proposed indication?

FDA Response:

The ACQ score has not been used by the Agency as an endpoint on which to base regulatory decisions. You will need to provide validation of this patient-reported outcome instrument if you intend to use the ACQ as an endpoint to support an indication. For additional information on patient reported outcome instruments, refer to the Guidance for Industry "Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims."

Discussion:

Cephalon acknowledged the lack of validation data in the briefing package and noted that the endpoint will be validated.

5. The number of clinical asthma exacerbations per patient from baseline to end-of-treatment is proposed as the primary efficacy variable in the clinical asthma exacerbation study. Does the Agency concur with the selection of this primary variable and the overall design of this study to support the proposed indication?

FDA Response:

The general concept and proposed duration appear reasonable. However, there is no universally accepted definition of asthma exacerbation; the adequacy of the proposed endpoint and the clinical relevance of the treatment difference will be a review issue. We note that the proposed definition is based on subjective decisions made by the healthcare provider or patient. Since the decision to initiate oral corticosteroids and emergency care may vary widely, we recommend that the definition of asthma exacerbation include objective criteria as well, such as spirometry or peak flows, rescue albuterol use, etc. In general, we recommend that evaluation of asthma exacerbation take into account the severity, duration, and number of exacerbations. Because of the complexity of this endpoint, our review of a submitted application will examine the totality of the data presented regarding asthma exacerbations.

Discussion:

Cephalon acknowledged the need to provide objective criteria for the definition of asthma exacerbations and noted that they intend to refer to the Xolair program. The Agency cautioned Cephalon regarding this approach, noting that the definition of exacerbations used in the Xolair program is not necessarily standard. The Agency recommended Cephalon refer to information regarding exacerbations/worsening of asthma contained in the product labels of combination products for asthma.

6. Does the Agency concur with the proposed safety measures in the Phase 3 studies?

FDA Response:

Given the proposed mechanism of reslizumab and what is known regarding the biological activity of eosinophils, the clinical program should address target-related safety concerns (e.g. immunoregulation, malignancy, parasitic infections). In addition, we note that you only plan on collecting ECG data in the pulmonary function trials if a patient has not had an ECG within 2 months prior to study enrollment. We recommend ECG assessments throughout the Phase 3 program.

Discussion:

Cephalon stated that safety measures will include electrocardiograms at baseline and at each visit. Regarding the Agency's statement concerning target-related safety issues, Cepthalon replied that they will conduct careful general safety monitoring. The Agency replied that they will need to address target-related safety concerns in their application.

7. Consistent with ICH-E1A recommendations, it is anticipated that the total number of individuals treated with reslizumab will be about 1500, including all short-term exposure (doses between 0.3 mg/kg and 3.0 mg/kg), at the time of BLA filing. Does the Agency concur that this total can be comprised of patients

from the proposed Phase 3 program and the patients (adult and pediatric) from the previous reslizumab trials conducted by Ception Therapeutics, Inc. and Schering Corporation?

FDA Response:

The adequacy of the safety database will depend on the totality of the data. Additional safety information may be required depending on the nature of the safety findings observed for reslizumab, taken in the context of the proposed disease population and expected duration of treatment.

Discussion:

The Agency noted that for monoclonal antibodies, animal toxicity information may be of limited relevance, and robust human data is needed. The Agency noted that the safety profile is expected to be appropriate for patients with asthma, which is a chronic but generally not life-threatening condition. The Agency suggested that Cephalon refer to the clinical programs for non-biologic drug products approved for asthma for guidance on the size and extent of the safety database, which in many cases exceeded ICH-E1A recommendations..

8. At the time of BLA submission or, at the latest, at the time of the four-month safety update, clinical safety data will be available from a minimum of 300 patients treated with reslizumab for at least 6 months and 100 patients treated with reslizumab for one year, including data from study in pediatric patients with eosinophilic esophagitis. Does the Agency concur that this would be an acceptable clinical safety data package for BLA filing?

FDA Response:

See our Introductory Comment. All data to support the BLA should be included at the time of submission.

9. Cephalon intends to seek initial BLA approval for adults and adolescents (≥ 12 years of age). Does the Agency concur that, subject to an acceptable pediatric plan, initial BLA approval could be granted prior to completion of assessment in any additional pediatric age groups?

FDA Response:

While your proposal appears reasonable, decisions about the deferral of pediatric study requirements are made during the review of the BLA.

Statistical Questions:

10. [redacted] (b) (4) ***Does the Agency concur with this approach?***

FDA Response:

[redacted] (b) (4) (b) (4) *this approach is not acceptable* [redacted] *. In your statistical analysis plan, discuss potential mechanisms which may cause FEV1 data to be missing, and how those mechanisms affected your selection of the primary analysis method. We also recommend that you outline additional analyses to gauge the sensitivity of your primary analysis method to violations of the assumed missing data mechanism. In addition, provide a plan on how you will integrate and explain the results from all these sensitivity analyses; in particular, if the results are in different direction from the result of the primary analysis.*

We also recommend that the reasons for discontinuation be clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent', etc. If a patient is 'lost to follow-up,' you should provide a plan for attempting to contact the patient so that a more informative category can be assigned. "

In your statistical analysis plan, discuss your approach in handling missing data for the ACQ endpoint (Studies 3083 and 3081).

Discussion:

Cephalon acknowledged the Agency's comment that [redacted] (b) (4) (b) (4) is unacceptable. [redacted]

In more general terms, the Agency noted that the National Academy of Sciences has been studying the issue of missing data and has recommended that protocols explicity address the assumptions underlying proposed estimands, the models used to estimate them, and any imputation methods for missing data. Protocols should include plans to test underlying assumptions and provide plans for sensitivity analyses and/or models for the case when the assumptions are not met. Protocols should also include plans to reduce

missing data by including procedures to capture data on patients who discontinue study medication or withdraw from the study. The reasons for discontinuation should be clearly documented.

11. The primary analysis for the study evaluating the frequency of clinical asthma exacerbations (CAEs) as the primary efficacy variable will be based on all treated patients. The number of CAEs per patient will be analyzed with a generalized linear model for negative-binomial data. For patients who withdraw early, an adjusted number of CAEs will be imputed from the recorded number of CAEs plus an estimate made on the basis of study treatment time remaining and the mean CAE frequency for completers in the treatment group. Does the Agency concur with this approach?

FDA Response:

In your synopsis, you propose to adjust the total number of CAEs for patients who withdraw early by assuming that these patients will have an additional number of CAEs after they dropout depending on their observed CAE rate and the time they remained in the study. This approach appears reasonable, except that your assessment for statistical significance of treatment effect will be based on more exacerbations than were actually observed, inflating the Type I error in your inference of treatment effect. Instead of adjusting the number of CAEs for patient who withdraws early, we recommend that you use a negative binomial regression model with an "offset" to account for different lengths of time each patient spends in the study. We also recommend that you include overdispersion in your model to account for potential heterogeneity in exacerbation rates between patients.

Discussion:

Cephalon noted that they agree with the Agency and will do as recommended.

Clinical Pharmacology Question:

12. Sparse samples for pharmacokinetics will be collected in the Phase 3 efficacy trials. These data will be used to characterize the pharmacokinetics of reslizumab and an attempt will be made to correlate systemic exposure with measures of safety and/or response. Does the Agency concur that this approach is adequate to support the clinical development program and BLA filing for the proposed indication?

FDA Response:

We generally agree that you may conduct sparse pharmacokinetic sampling in the Phase 3 efficacy trials. However, we noticed the pharmacokinetic information submitted in the background package is limited. Based on the submitted pharmacokinetics summary, you indicated linearity was confirmed in asthma patients in the dose range of 0.03 to 1.0 mg/kg after single dose. You also indicated (b) (4) *but it is not mentioned in the package if similar findings were observed for asthma patients. In addition, we note that trial Res-5-0010 evaluated only the 3.0 mg/kg dose and the proposed Phase 3 trials do not include further dose exploration. . Therefore, we recommend that you further characterize the dose response relationship in the population of interest by exploring more dose regimens. We also recommend that you characterize the PK of your product in your target patient population after both single and multiple doses.*

Discussion:

Cephalon stated that they do have additional PK data which are not included in this submission package and they intend to address these questions raised by the Agency in their BLA application.

Nonclinical Pharmacology/Toxicology Question:

13. Does the Agency concur that the preclinical safety program is adequate to support the clinical development program and BLA filing for the proposed indication (b) (4) ***?***

FDA Response:

We do not concur. The rationale (b) (4) *provided on page 114 of the meeting package is inadequate. We note that the mouse is a relevant species for reslizumab. In the 6-month intravenous toxicology study, it appears that exposure to reslizumab was maintained throughout the study. Decreased eosinophil counts were observed in the study. Recent publications (e.g., Journal of Immunology 2007; 178: 4222-4229 and Journal of Leukocyte Biology 2006; 79: 1131-1139) suggest roles for IL-5 and eosinophils in tumor immune surveillance.* (b) (4) *conduct a 2-year carcinogenicity study with reslizumab in mice.*

(b) (4)

With the exception of the assessment for carcinogenic potential, the preclinical safety program appears generally adequate to support the clinical development program and BLA filing for the proposed indication. Provide all nonclinical pharmacology and toxicology studies with the submission of the Phase 3 clinical protocols. If the frequency of clinical dosing is increased, additional supporting nonclinical toxicology studies may be required.

Discussion:

Cephalon stated that they plan to submit a White Paper with literature references (b) (4) The Division noted that the material provided in the meeting package was inadequate (b) (4) . Further, the ECAC concurred on this issue. Cephalon plans to address these issues in the White Paper and asked about the review time for the submission. The Division stated that the review time could be relatively quick (e.g., 1 month dependent on workload). Cephalon asked if it was judged that a carcinogenicity study would be required, could a transgenic mouse model be considered. The Division stated that a transgenic mouse model could be considered, provided that there was appropriate justification. The Division stated if a carcinogenicity study was required, Cephalon should provide an appropriate dose range finding study, a dose selection proposal, and draft carcinogenicity study protocol for review by the Division and ECAC.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ACTION ITEMS

There are no action items.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts provided at the meeting.

Drafted by: CCJ/ September 13, 2010

Initialed: Limb/ September 15, 2010
Pippins/ September 15, 2010
Robison/ September 15, 2010
Topper/ September 15, 2010
Xu/ September 15, 2010
Abugov/ September 14, 2010
Davi/ September 14, 2010
Chowdhury/ September 16, 2010

Finalized: CCJ/ September 16, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-101399	GI-1	CEPHALON INC	Reslizumab ((b) (4)

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/s/

COLETTE C JACKSON
09/16/2010

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

LATE-CYCLE MEETING MINUTES

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for reslizumab.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 23, 2015.

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}

Banu Karimi-Shah, M.D.
Cross Disciplinary Team Leader
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

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 23, 2015, 4PM to 5 PM EST
Meeting Location: White Oak, Building 22, Conference Room 1419

Application Number: BLA 761033
Product Name: Reslizumab
Indication: Asthma
Sponsor/Applicant Name: Teva Branded Pharmaceutical Products R&D, Inc.

Meeting Chair: Banu Karimi-Shah, M.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

Office of Drug Evaluation II
Curtis Rosebraugh, M.D., Director

Division of Pulmonary, Allergy, and Rheumatology
Badrul A. Chowdhury, M.D., Ph.D., Director
Lydia Gilbert-McClain, M.D., Deputy Division Director
Sally Seymour, M.D., Deputy Director for Safety
Banu Karimi-Shah, M.D., Cross Disciplinary Team Leader
Kathleen Donohue, M.D., Clinical Reviewer
Carol Galvis, Ph.D., Pharmacology/Toxicology Reviewer
Colette Jackson, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Clinical Pharmacology II
Yunzhao Ren, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics
Freeda Cooner, Ph.D., Statistical Team Leader

Office of Biotechnology Products
Maria Teresa Gutierrez, Ph.D., Product Quality Application Team Lead
Tracy Denison, Ph.D., Product Quality Reviewer
Ramesh Potla, Ph.D., Product Quality Reviewer
Joao Pedras Vasconcelos, Ph.D., Immunogenicity Reviewer

Office of Process and Facilities
Patricia Hughes, Ph.D., Office of Compliance
Lakshmi Narasimhan, Ph.D., Microbiology Reviewer

Bo Chi, Ph.D., Microbiology Team Leader
Thuy Nguyen, Ph.D., Facility Reviewer
Peter Qui, Ph.D., Branch Chief, Division of Inspectional Assessment

Office of Surveillance and Epidemiology
Margie Goulding, M.D., Lead Epidemiologist,
Jasminder Kumar, Pharm.D., Safety Evaluator, Division of Risk Management
Michael Sinks, Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Peggy Khorrami, Independent Assessor

TEVA PHARMACEUTICAL ATTENDEES
Christine Kampf, Sr. Manager, Regulatory Affairs Global Branded Products
Kenneth Bonk, Sr. Director, Regulatory Affairs Global Branded Products
James Zangrilli, MD, Sr. Director, Clinical Project Leader
Tushar Shah, MD, VP, Global Respiratory R&D
Yael Shalit, MD, Director, Pharmacovigilance Safety Physician
Judith Zander, Global Head, Safety Physicians
Mary Bond, MS, MBA, Director, Clinical Pharmacology
Mary Peterman, Sr. Director, Project Champion
Linglong Zou, PhD, Director, Experimental Immunology and Global Bioassays and Technology
Laurie Pukac, PhD, Director, Global Bioassays and Technology
Sivan Weiss, MSc, Associate Director, Global Biostatistics
Michael Vanderwerf, Director, CMC Regulatory Affairs
Jason Bock, VP, Global CMC Biologics
Anat Sakov, Director, Statistics, Head of Respiratory and Biosimilars
Brittany Bentz, Senior Associate, Regulatory Affairs
Susan Franks, Senior VP, Regulatory Affairs
Laurie Pukac, PhD, Director, Global Bioassays and Technology
Patrick Liu, MD, PhD**,** VP, Global Bioassays

1.0 BACKGROUND

BLA 761033 was submitted on March 29, 2015 for Cinqair (reslizumab).

Proposed indication(s): Asthma

PDUFA goal date: March 30, 2016

FDA issued a background package in preparation for this meeting on November 18, 2015.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes

Reference ID: 3862596

Welcome, Introductions, Ground rules, Objectives of the meeting

2. ***Discussion of Substantive Review Issues – 10 minutes***
   - ***Limitations of dose-ranging in the clinical development program***
   - ***Efficacy in subgroups (US, adolescents)***
   - ***Safety signals***
     - ***Anaphylaxis – to include a discussion of product issues (alpha-gal)***
     - ***Muscle toxicity***

   - ***Satisfactory evaluation of all manufacturing facilities is required for BLA approval. The responses to 483 observations issued during the pre-license inspection at (b) (4) are currently under review.***

Discussion:
The FDA stated that the satisfactory evaluation of manufacturing facilities for the reslizumab product is still under review.

3. ***Discussion of Minor Review Issues – 5 minutes***

4. ***Additional Applicant Data – 5 minutes***
   - ***Received response to information request re: anaphylaxis and this is under review***

5. ***Information requests – 5 minutes***
   a. ***CMC IR sent November 16, 2015***
   b. ***A product quality micro IR will be sent out this week***

6. ***Discussion of Upcoming Advisory Committee Meeting – 10 minutes***
   - ***Proposed indication – discussion at advisory committee will be focused on asthma with specific indication to be defined during labeling negotiations***

Discussion:

The FDA informed Teva that the proposed indication as submitted was not included in the discussion materials submitted to the Advisory Committee (AC). The FDA will work with Teva after the AC meeting on the exact wording of the indication.

The FDA acknowledged Teva's email dated November 17, 2015, which stated Teva has identified a commercially available assay to detect anti-alpha gal IgE antibodies in patient serum

Reference ID: 3862596

at the advisory committee and had sent samples for testing from identified cases of anaphylaxis. The FDA requested that Teva provide a caveat to the AC committee that the FDA will not have had the opportunity to review the anti-alpha gal IgE antibody assay data to be presented at the AC meeting. Teva stated they intend to provide the data to FDA prior to the AC meeting. The FDA asked Teva about their intentions with the assay result data. Teva stated they will confirm the assay results with the clinical evidence provided from the assigned site investigator. The FDA requested that Teva provide the geographical location along with patient results from the anti-alpha gal IgE assay. Teva stated they have identified errors to the AC briefing document and intend to send an errata document to the FDA to clarify any errors.

The FDA stated that the anaphylaxis safety signal will be discussed at the AC meeting. Anaphylaxis criteria are commonly built into most development programs for anti-IL5 products which include specific time points and qualitative criteria for handling the adverse event. Teva did not have such criteria built into their development plan for reslizumab and therefore adjudication was needed, which is subopitmal. The FDA voiced concern that there are anaphylaxis adverse events that may not have been captured.

7. Review Plans – 5 minutes

- ***Anaphylaxis information request response***
- ***Further review plans pending Advisory Committee Input***

8. Wrap-up and Action Items – 5 minutes

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

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.

Reference ID: 3862596

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/s/

BANU A KARIMI SHAH
12/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761033

LATE CYCLE MEETING
BACKGROUND PACKAGE

Teva Branded Pharmaceutical Products R&D, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Senior Manager, Regulatory Affairs

Dear Ms. Kampf:

Please refer to your Biologics License Application (BLA) dated March 29, 2015, received March 30, 2015, submitted under section 351(a) of the Public Health Service Act for Reslizumab.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 23, 2015. Attached is our background package, including our agenda, for this meeting.

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, MD, PhD
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

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: November 23, 2015, 4PM to 5 PM EST
Meeting Location: White Oak, Building 22, Conference Room 1419

Application Number: BLA 761033
Product Name: Reslizumab
Indication: Asthma
Sponsor/Applicant Name: Teva Branded Pharmaceutical Products R&D, Inc.

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

- Limitations of dose-ranging in the clinical development program
- Efficacy in subgroups (US, adolescents)
- Safety signals
    - Anaphylaxis – to include a discussion of product issues (alpha-gal)
    - Muscle toxicity

Reference ID: 3848513

- Satisfactory evaluation of all manufacturing facilities is required for BLA approval. The responses to 483 observations issued during the pre-license inspection at (b) (4) are currently under review.

ADVISORY COMMITTEE MEETING

Date of AC meeting: December 9, 2015

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: November 18, 2015

Potential questions and discussion topics for AC Meeting are as follows:
Please refer to AC briefing document

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:
http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes
   - Limitations of dose-ranging in the clinical development program
   - Efficacy in subgroups (US, adolescents)
   - Safety signals
     - Anaphylaxis – to include a discussion of product issues (alpha-gal)
     - Muscle toxicity
     - Satisfactory evaluation of all manufacturing facilities is required for BLA approval. The responses to 483 observations issued during the pre-license inspection at (b) (4) are currently under review.

Reference ID: 3848513

3. Discussion of Minor Review Issues – 5 minutes

4. Additional Applicant Data – 5 minutes
    - Received response to information request re: anaphylaxis and this is under review

5. Information requests – 5 minutes
    - CMC IR sent November 16, 2015
    - A product quality micro IR will be sent out this week

6. Discussion of Upcoming Advisory Committee Meeting – 10 minutes
    - Proposed indication – discussion at advisory committee will be focused on asthma with specific indication to be defined during labeling negotiations

7. Review Plans – 5 minutes
    - Anaphylaxis information request response
    - Further review plans pending Advisory Committee Input

8. Wrap-up and Action Items – 5 minutes
    - No further action items
    - Additional questions from the Sponsor

Reference ID: 3848513

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/s/

BADRUL A CHOWDHURY
11/18/2015