

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125431Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

NDA/BLA#: 125431 Supplement Number: N/A NDA Supplement Type (e.g. SE5): _____
Division Name: DMEP PDUFA Goal Date: April 15, 2014 (original PDUFA date extended 3 months) Stamp Date: 1/11/2013

Proprietary Name: Tanzeum (proposed)
Established/Generic Name: albiglutide
Dosage Form: for injection, for subcutaneous use
Applicant/Sponsor: GSK

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

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

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

Indication: Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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 failed ^Δ	
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. <u>0</u> mo.	<u>9</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

justification):

Not feasible:

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

* Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

 Justification attached.

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

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

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

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	10 yr. 0 mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____**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 failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

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

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

If there are additional indications, please 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/

RAYMOND S CHIANG
01/07/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # BLA # 125431	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Tanzeum Established/Proper Name: albiglutide for injection, for subcutaneous use Dosage Form: For injection: 30 mg and 50 mg in a single dose pen		Applicant: GlaxoSmithKline LLC Agent for Applicant (if applicable):
RPM: Raymond Chiang		Division: DMEP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 15, 2014</u> 		<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> Received
❖ 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, (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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

NDAs: Subpart H
 Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

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

Subpart I
 Approval based on animal studies

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: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input checked="" type="checkbox"/> Yes, dates Facility information sheets sent to Vicky Carter on 3.13.14
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> 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 (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) 4.15.14
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> • Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included (see label attached to Approval letter)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included (See Medication Guide attached to the Approval letter)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included (See carton and container labels attached to the approval letter)
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s)) 	8.2.13; 4.12.13 8.2.13; 4.12.13
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 3.19.13 DMEPA: <input type="checkbox"/> None 2.19.14, 10.24.13 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input type="checkbox"/> None SEALD: <input type="checkbox"/> None 4.11.14 CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	4.3.14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>1.22.14</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	2.24.14, 12.6.13, 11.22.13, 11.14.13, 11.5.13, 10.28.13, 10.25.13, 7.30.13 4.9.13, 3.22.14
<ul style="list-style-type: none"> ❖ 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) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> No mtg Preliminary comments sent on 10.9.12; the Pre-BLA was subsequently cancelled by sponsor <input type="checkbox"/> No mtg 8.12.08 <input type="checkbox"/> N/A 6.26.13 <input type="checkbox"/> N/A 1.13.14
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4.15.14
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4.14.14
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4.11.14
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 4.14.14
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review 11.4.13 <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	See page 27 of clinical review dated 11.4.13

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DEpi review 10.2.14; CDRH 9.4.13; CDRH (human factors) 9.7.13; QT-IRT review 8.5.13; CDRH 1.27.14
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	4.14.14 <input type="checkbox"/> None OPDP 3.19.14; OSE 4.11.14; 3.18.14, 10.16.13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 4.7.14
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 10.25.13
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10.25.13; CV stats 9.3.13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12.3.13
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested 12.5.13
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7.25.13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 4.11.14; 2.20.14; 2.14.14; 12.17.13
❖ Microbiology Reviews		<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		CMC Micro 4.10.14; CMC Micro (DS) 12.18.13; CMC Micro (DP) 1.6.14
<input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See page 7 of Product Quality review dated 12.17.13
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		See page 7 of Product Quality review dated 12.17.13
❖ Facilities Review/Inspection		
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input checked="" type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

From: Chiang, Raymond
To: [Paul Talierco \(paul.a.talierco@gsk.com\)](mailto:paul.a.talierco@gsk.com); [Susan Watts \(susan.l.watts@gsk.com\)](mailto:susan.l.watts@gsk.com); [Sharon Shapowal \(Sharon.W.Shapowal@gsk.com\)](mailto:Sharon.Shapowal@gsk.com)
Subject: Re: CMC advice -- albiglutide BLA
Date: Monday, February 24, 2014 10:35:00 AM

Hi Paul,
This is f/u advice from CMC for a PMC request discussed for the DP during the Late Cycle meeting .
Please confirm receipt.
Thanks,
Ray

You proposed to (b) (4)
completion of the Registration Stability and Process Qualification batches stability programs.
The agency accepts your proposal. However, the agency recommends you to use the (b) (4)

Raymond S. Chiang, MPT, MS, MS
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Email: Raymond.Chiang@fda.hhs.gov
phone: 301-796-1940

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/s/

RAYMOND S CHIANG
02/24/2014

From: Chiang, Raymond
To: [Susan Watts \(susan.l.watts@gsk.com\)](mailto:susan.l.watts@gsk.com); [Sharon Shapowal \(Sharon.W.Shapowal@gsk.com\)](mailto:Sharon.Shapowal@gsk.com); [Paul Talierco \(paul.a.talierco@gsk.com\)](mailto:Paul.Talierco@gsk.com)
Subject: FW: IR for STN125431
Date: Friday, December 06, 2013 2:15:00 PM
Attachments: [STN125431 IR 12-6-13.pdf](#)

Hi Susan and Paul,
See attached IR from the FDA CMC Micro reviewer . She requests to have the email response back by 12/12.
As always, please confirm receipt of email.

Thanks,
Ray

CMC quality microbiology information request for BLA STN125431/0:

1. With regard to your response in amendment dated 10/31/2013 (Sequence 37), the (b) (4)
[REDACTED] in Report GKAL-10-000421-1335 (Attachment 4, page 8 and 9). In contrast, the example used in the combined response to Items 15 and 16 (Page 5) showed that the (b) (4)
[REDACTED] Please explain the differences of the study results.
2. Please conduct studies to evaluate if the (b) (4)
[REDACTED] are pyrogenic in rabbits. In addition, a reliable DP endotoxin test should be established for product release. A path forward for pyrogen testing will have to be determined for future product release to market.

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/s/

RAYMOND S CHIANG
12/06/2013

From: Chiang, Raymond
To: [Susan Watts \(susan.l.watts@gsk.com\)](mailto:susan.l.watts@gsk.com); [Sharon Shapowal \(Sharon.W.Shapowal@gsk.com\)](mailto:Sharon.Shapowal (Sharon.W.Shapowal@gsk.com))
Subject: FW: Albigultide C & C labeling -- BLA 125431 --- DMEPA/OSE Comments to Applicant
Date: Friday, November 22, 2013 3:08:00 PM

Hi Susan,

See comments from DMEPA/OSE in response to your most recent C & C labeling submission (eCTD sequence 39). Please respond to these comments from OSE/DMEPA.

As always, please confirm receipt.

Thanks and have a great weekend,

Ray

1. Replacement Carton Labeling

- a. DMEPA Comment: Provide additional differentiation between the 30 mg and 50 mg replacement labels because [REDACTED] (b) (4)

[REDACTED]

[REDACTED] This may help provide better differentiation between the strengths.

2. DMEPA Recommendation: Ensure that the image of the pen device accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.

GSK Response: The pen device image is a three-dimensional rendering of the pen device in its actual size; however, it is not the actual pen because we do not have actual pen photographs available yet. A photograph of the pen would be available once we have an approved label. If possible, GSK would prefer to keep this rendering rather than a photograph of the actual pen. Please comment.

DMEPA Comment: The current pen device image is acceptable.

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

/s/

RAYMOND S CHIANG
11/22/2013

From: Chiang, Raymond
To: [Susan Watts \(susan.l.watts@gsk.com\)](mailto:susan.l.watts@gsk.com); [Sharon Shapowal \(Sharon.W.Shapowal@gsk.com\)](mailto:Sharon.Shapowal (Sharon.W.Shapowal@gsk.com))
Subject: FW: BLA 125431 IR response
Date: Thursday, November 14, 2013 2:46:00 PM
Attachments: [IR for sponsor.doc](#)

Hi Susan,

See proposed responses to your questions regarding labeling for appendicitis, hypersensitivity, and cases of hepatocellular injury. You can respond to these during our next round of labeling negotiations.

As always, please confirm receipt of email.

Thanks,
Ray

Sponsor's Request 1:

Appendicitis: Non-fatal serious events of appendicitis occurred in 0.3% (6/2,116 subjects) compared to 0/2,284 among all comparators (placebo plus active comparators).

Could the review team please clarify

- Whether the statement is based on the Original BLA dataset or on the 120-Day Safety Update Report data cut?
- Do the subject counts reflect the collapsing of multiple MedDRA preferred terms (e.g., 'appendicitis' and 'appendicitis perforated')?

FDA Response: Appendicitis cases reviewed in support of the proposed labeling are described below:

ORIGINAL BLA DATASET

4 cases of appendicitis and 1 cases of perforated appendicitis occurred in albiglutide subjects (0.2%) vs. 0 in all comparators. Brief narratives of appendicitis events are delineated below.

- Subject 3779754986: 28-year old male on study day 210 experienced severe **appendicitis** with pathology revealing acute gangrenous appendicitis and periappendicitis.
- Subject 3644755986: 61-year old female experienced severe **perforated appendicitis** 222 days after the first dose of investigational product.
- Subject 1423486016: 40-year old female experienced acute suppurative **appendicitis** and underwent appendectomy on day 178 days.
- Subject 7661753988: 62-year old female developed acute phlegmonous ulcerative **appendicitis** with fibrotic/purulent periappendicitis on study day 653.
- Subject 3579753987: 59-year old female experienced severe **appendicitis** on study day 300.

4MSU (APPENDICITIS EVENTS)

There was one additional case of appendicitis in the albiglutide group vs. 0 in all comparators.

- Subject 3774753980: 41 year old female developed acute **appendicitis** on study day 937.

CUMULATIVE (APPENDICITIS EVENTS)

Overall non-fatal serious events of appendicitis occurred in a higher proportion of albiglutide treated subject 0.2% (5/2116) compared to 0 in all comparators. In addition there was 1 case of perforated appendicitis in the albiglutide group.

Sponsor's Request 2:

The sponsor requested that the review team identify the specific cases, by masked PID, that led them to the conclusions reflected in proposed labeling (highlighted text):

1. Cases of hypersensitivity as reflected in

4.2 Hypersensitivity

(b) (4)

(b) (4)

(b) (4)

FDA Response: The following cases were reviewed in support of the proposed labeling for hypersensitivity:

Anaphylaxis:

Subject 1001179014: 50-year old female experienced an adverse event categorized as a systemic allergic reaction. However based on review of the narrative it appears the subject may have experienced an **anaphylactic reaction**. This is supported by the development of a diffuse rash within 90 days of starting investigational product. In addition the subject experienced a resolution of symptoms with study drug withdrawal and a recurrence of rash with shortness of breath upon rechallenge with albiglutide.

Subject 3432754986: 69 year old female experienced swelling of the tongue and shortness of breath categorized as an **anaphylactic reaction** on study day 733 days. The subject tested negative for the antibody to albiglutide.

Angioedema:

Three subjects in the albiglutide arm had single events of angioedema and are described below.

Subject 1001486015: 65-year-old female with a medical history of hyperlipidemia and hypertension (treated with lisinopril 10 mg daily), experienced swelling **of the lips and tongue** and renal insufficiency on study day 59.

Subject 3501754987: 59-year old male experienced **tongue swelling** and **angioedema** 717 days after the first dose of albiglutide requiring treatment with IV steroids

Subject 3699757986: 55-year old male experienced mild urticaria and mild lip **angioedema** 413 days after the first dose of investigational product.

Subject 5701179009: 51 year old man with hypertension and hyperlipidemia developed **uvula edema** on study day 101.

2. *Cases of hepatocellular injury as reflected in*

6.1 Clinical Trials Experience

(b) (4)



FDA Response: The following cases were reviewed in support of the proposed labeling of liver injury accompanied by potential cholestatic effects:

Subject 1028179043: 61-year old female experienced **elevated liver lab findings** (ALT 499 U/L, AST 511 U/L, T. bili 1.3 mg/dl, GGT 581 U/L) the same day as the second dose of albiglutide (Day 8).

Subject 3599757986: 71-year old male developed transient **increases of ALT** (492 U/L), AST (168 U/L) and GGT (505 U/L) on study day 455.

Subject 3663753989: 53 year old female experienced an acute transient **rise in liver test results** on study day 15 (ALT: 441 U/L, AST: 222 U/L, GGT: 482 U/L, ALP: 212 U/L, T. bili: 0.5 mg/dl).

Subject 1200179009: 52-year old female experienced **sudden rise of serum liver lab findings** (ALT 356 U/L, AST 77 U/L, GGT 333 U/L, ALP 132 U/L) on the same day of the 6th dose of albiglutide administration.

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

/s/

RAYMOND S CHIANG
11/14/2013

From: Chiang, Raymond
To: ["Paul Talierco"](#)
Cc: [Susan Watts](#); [Sharon Shapowal](#)
Subject: CDRH information requests ---- BLA 125431
Date: Tuesday, November 05, 2013 4:03:00 PM

Hi Paul,

See additional information requests related to biocompatibility from CDRH. As always, please confirm receipt.

Thanks,

Ray

1. In ICC1300526, a summary of the cytotoxicity data was provided. However, the data for the sensitization and intracutaneous or irritation studies were not provided. We need full test studies and protocols for the cytotoxicity, sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO-10993-5 Cytotoxicity, ISO 10993-10 Irritation or intracutaneous and Sensitization.
2. Pyrogen testing should be completed because the device will have short contact with blood.
 - i. Please submit a complete report for bacterial endotoxin estimation expressed in endotoxin units per milliliter, i.e., EU/mL, according to Limulus Amoebocytes Lysates (LAL) test for endotoxins per ANSI/AAMI ST72:2002 Bacterial endotoxins-Test methodologies, routine monitoring, and alternatives to batch testing.
3. During the review, we were unable to find the Material Safety Data Sheets for the materials listed in the tables under the Device Description. Provide additional information regarding the materials used to manufacture the device.

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/s/

RAYMOND S CHIANG
11/05/2013

From: Chiang, Raymond
To: [Susan Watts \(susan.l.watts@gsk.com\)](mailto:Susan.Watts@gsk.com); [Sharon Shapowal \(Sharon.W.Shapowal@gsk.com\)](mailto:Sharon.Shapowal@GSK.com)
Subject: Re: Albiglutide label
Date: Monday, October 28, 2013 1:30:00 PM
Attachments: [albiglutide draft label sent to GSK_10.28.13.doc](#)

Hi Susan,
See attached label (PI/MedGuide) for Albiglutide (BLA 125431)

Please accept all FDA edits that you agree with. So, the document should only show in tracked changes (1) any new edits GSK has made to our prior edits and (2) any new edits from GSK unrelated to our prior edits.

To help avoid confusion, please delete outdated comments and formatting bubbles. Please leave only comment and formatting bubbles relevant to the next round of labeling negotiations in the label. When you add a comment bubble, please state " GSK response to FDA change or GSK Comment." This will be useful for showing which edits come from FDA vs. which edits were from GSK.

You only need to add a comment bubble responding to our bubbles in cases where you disagree with our comment or if you want to provide additional information you want us to consider. So, not all comment bubbles necessarily need to have an accompanying response comment bubble from you.

Please email your revised label (tracked-changes Word versions) to us by COB, Monday, November 4, 2013.

In addition, we have the following comments (see below in black font) from our OSE colleagues associated with your PI, IFU, and carton and container labels. This was a straight cut and paste from a document OSE provided to me.

3. RECOMMENDATIONS

Based on OSE's evaluation, we recommend the following revisions be implemented prior to approval of this product:

3.1 Wait Time

- Revise the wait time for dissolving the medication to 30 minutes for both strengths (30 mg and 50 mg). Currently, the wait time is 15 minutes for the 30 mg strength and 30 minutes for the 50 mg strength. The Usability Study results demonstrated that three participants failed to wait 30 minutes because they assumed that the wait time for the 50 mg is the same as the 30 mg strength. Failure to wait 30 minutes for the 50 mg dose to dissolve can result in delivery of an underdose due to either low concentration dose volume or needle clogging. If this change is feasible, revise the Prescribing Information, IFU and carton labeling accordingly.
- If it is not feasible to revise the wait time to 30 minutes for both strengths, then add the wait time statement or diagram to the 30 mg and 50 mg container labels and carton labeling, and retest the wait time scenario with at least 15 patients and 15 HCPs to validate that users will wait for the product to dissolve before

administering. Revising the labels and labeling may serve as an additional prompt for users who may not read the IFU or pay attention to the carton labeling - similar to the participants in the Usability Study who either skimmed or did not read the IFU for the 50 mg strength and assumed the wait time was the same as the 30 mg.

3.2 Container Label

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.

3.3 Carton Labeling

3.3.1 Commercial Packaging

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Ensure that the image of the pen device accurately represents the actual size, shape, color, and imprint of the commercial product and is not a schematic or computer-generated image. In addition, this image should be less prominent than the proprietary name, established name and strength.
- Remove the (b) (4) on the primary display panel as this information is contained on the back panel. This will help reduce clutter and increase readability of other important information such as proprietary name, established name and strength.

3.3.2 Sample Packaging

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other

printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.

- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Relocate the statement “Sample- Not for Sale” to the primary display panel so that it is clear this package is not for commercial sale and it will differentiate it from the Replacement carton labeling.

3.3.3 Replacement

- Revise the presentation of the proprietary name from all uppercase (e.g. TRADENAME) to title case (e.g. Tradename) to increase readability.
- Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name.
- Use the same color scheme presentation used in the commercial carton labeling (i.e. strength presentation in color). As currently presented, the replacement carton is in (b) (4) making it difficult to differentiate between the two strengths.
- Remove or reduce the size of the graphic to the left of the proprietary name as it appears more prominent than the proprietary and established names. The proprietary and established names and strength should be the most prominent information on the labels.
- Relocate the statement “Replacement Pen- Not for Sale” to the primary display panel so that it is well differentiated with the Sample carton labeling.

3.4 Instructions for Use (IFU)

- The IFU was revised to increase the prominence of the wait time (30 minutes) for the 50 mg dose. However, we did not receive results from another validation study that demonstrated this revision was effective. Therefore, we recommend retesting of the wait time scenario to ensure that the revisions to the IFU in addition to the container label changes are sufficient to mitigate or prevent the failure to correctly accomplish this critical task.

3.5 Prescribing Information (PI)

- Delete the section entitled “Alternate Method of Reconstitution (Healthcare Professional Use Only).” The information provided in this section conflicts with the information provided in the IFU and Human Factors Validation Test regarding wait times. Specifically, your “User Tasks and Clinical Impact Table” on page 46 of the Human Factors Validation Test Report states that a user (b) (4)

Additionally, you did not provide data to demonstrate the instructions for healthcare providers "Alternate Method of Reconstitution" are validated and that healthcare providers perform "appropriate swirling for one minute."

Please do not hesitate to call or email if you have any questions.

Please confirm receipt of email.

thanks,
ray

Raymond S. Chiang, MPT, MS, MS
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Email: Raymond.Chiang@fda.hhs.gov

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

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/s/

RAYMOND S CHIANG
10/28/2013

From: Chiang, Raymond
To: ["Susan Watts"](#)
Cc: [Sharon Shapowal](#)
Subject: RE: Albiglutide REMS
Date: Friday, October 25, 2013 4:43:00 PM
Attachments: [Redlined REMS \(2\).doc](#)
[albiglutide REMS letter template Printed.docx](#)
[albiglutide_email_template_professional_society_\(2\).docx](#)
[albiglutide REMS letter template Printed_prof_soc.docx](#)
[template_for_REMS_albiglutide_Webpage.docx](#)
[albiglutide_email_template_HCPs_\(2\).docx](#)
[image002.png](#)

Hi Susan,

See below comments from our OSE colleagues in response to your proposed albiglutide REMS. As always, please confirm receipt of email.

Thanks,

Ray

We acknowledge your submission of a proposed REMS for albiglutide (December 20, 2012) and have the following revisions and comments:

- 1) At this point in the BLA review process, MTC and pancreatitis are the only risks to be included in this REMS; evidence to support inclusion of other serious risks in the REMS may surface during the remaining BLA review process.
- 2) Goal statement: the goal statement was restated for clarity as follows:
 - i) The goal of the TRADENAME REMS is to mitigate the risk of pancreatitis and the potential risk of medullary thyroid cancer associated with TRADENAME by:
 - (1) informing healthcare providers (HCP) about the risk of acute pancreatitis associated with TRADENAME
 - (2) informing HCP about the potential risk of medullary thyroid cancer associated with TRADENAME.
- 3) Key albiglutide CP REMS messages must be consistent with the product's final labeling and may include the following, as applicable:
 - a) Albiglutide is potentially associated with the risk of MTC
 - b) HCPs must consider other anti-diabetic therapies in patients with a personal or family history of MTC, and in patients with Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2).
 - c) Albiglutide is associated with the risk of acute pancreatitis.
 - d) Patients should be monitored for signs and symptoms of pancreatitis when treated with albiglutide.
 - e) If pancreatitis is suspected, albiglutide should be discontinued.
 - f) If pancreatitis is confirmed, albiglutide should be discontinued and not be restarted.
 - g) Patients must be counseled to be aware of the signs and symptoms of acute pancreatitis (i.e., severe and persistent abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting), and the signs and symptoms of MTC, and of the importance of reporting these to their physicians as soon as possible.
- 4) REMS document – a revised version of the REMS document is attached.

5) Communication Plan – the REMS should include the following communication tools:

i) REMS letters, REMS Factsheet, and a REMS website.

- (1) REMS Letters—Replace the use of a [REDACTED] (b) (4) [REDACTED] with concise, risk-focused REMS letters addressed to HCPs and relevant Professional Societies. FDA proposes having the REMS letters formatted in two different ways: print and electronic versions. The electronic version of the REMS letters should be email- and handheld device-friendly. The objective of these changes is to improve the communication of the risk message among the growing HCP population of hand-held device users. The subject of the emails should be “Risk of Medullary Thyroid Carcinoma and Acute Pancreatitis with Eperzan (albiglutide)”. The outside of the mailed envelopes should state: "FDA Required REMS Safety Information: it should be printed in red, bolded, and a minimum size 14 font. It may be on two lines and should be boxed, for example:



See proposed print and electronic REMS letter templates attached.

- (2) [REDACTED] (b) (4) [REDACTED]—Replace proposed [REDACTED] [REDACTED] with a new REMS Factsheet for HCPs. This REMS Factsheet must be in a user-friendly format, including coloring, and any logos from Eperzan's REMS program; include bullets, boxes, and bold text to highlight important information; should have plenty of white space and a font size of at least 12; be printed on thicker card stock paper; be only one sheet with information on both sides of paper and heading should read: FDA Required Eperzan REMS Safety Information.

Key messages to include on fact sheet include: boxed warning information, including risk of medullary thyroid carcinoma, risk of acute pancreatitis, contraindications, patient counseling on symptoms of thyroid tumors and acute pancreatitis, and brief REMS explanation.

- (3) REMS Website—Ensure the REMS website, is independent of link to the promotional and/or commercial website and non-REMS materials about the product. Do not include a [REDACTED] (b) (4) [REDACTED]. The REMS website should also be accessible directly through a search engine. The REMS website, including all REMS materials (REMS letters, REMS factsheet) will be available for the duration of the REMS.

(i) Submit screen shots and actual layout for the Eperzan REMS

website

We remind you to use bullets, moderate white space, shorter line lengths, and fewer lines of text when possible when developing your website. The following is a link to helpful guidelines developed by HHS that you may consider in developing your website.

http://www.usability.gov/sites/default/files/documents/guidelines_book.pdf?post=yes

See proposed REMS website template attached.

- 6) Timetable for submission of REMS assessments – revise the timetable for submission of assessments of albiglutide REMS assessment reports to 18 months, 3 years, and 7 years from the date of the approval of the REMS. This will permit assessment of the 12-month communication, and is consistent with the assessment timelines described in the statute.
- 7) REMS assessment plan: the albiglutide REMS assessment report must include but not be limited to the following items—
 - a) REMS communication plan activities:
 - (1) Number of HCPs and professional societies targeted by the REMS.
 - (2) Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - (3) Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
 - (4) Date when REMS website went live and number of total and unique site visits during the assessment period.
 - b) Evaluation of HCPs’ understanding of:
 - (1) The potential risk of MTC
 - (2) The risk of pancreatitis
 - (3) The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.
 - (4) Identification and treatment of acute pancreatitis after initiation of albiglutide.
 - (5) Appropriate albiglutide patient population characteristics
 - c) Safety surveillance
 - (1) Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
 - (2) Evaluation and postmarketing case reports of pancreatitis
 - (3) Evaluation and postmarketing case reports of MTC
 - (4) Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals
 - d) The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification
 - e) The inclusion of REMS assessment report synopsis or executive summary is helpful in the Agency’s review of the REMS Assessment Reports.

- 8) Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.
- 9) Product marketing materials generally are not appropriate to educate about product risks.
- 10) Please submit all planned materials (e.g., proposed communications, education materials, and REMS website) identified within the plan that will be necessary to implement your proposal.
- 11) We recommend pre-testing all REMS materials.
- 12) Update the REMS Supporting Document to reflect all the changes to the REMS, REMS appended materials, and REMS assessment plan.
- 13) HCP survey: Submit for review the detailed plan you propose to use to evaluate prescribers' understanding about the safe use of albiglutide. You may submit the proposed plan after approval of the REMS; however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of albiglutide.
 - a) Recruit respondents using a multi-modal approach.
 - b) Explain how often you perform non-respondent follow-up or reminders. If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value. Explain how you select recruitment sites. Submit for review any recruitment advertisements.
 - c) Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of prescriber knowledge for each key risk(s).
 - d) Define the expected number of prescribers to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
 - e) Ensure the sample is demographically representative of the prescriber population regardless of the condition for which they prescribe it.
 - f) When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, and geographically.
 - g) List the inclusion criteria for prescribers.
 - h) Submit any screener instruments, and describe any quotas of sub-populations used.
 - i) Explain how you administer surveys and the intended frequency. Offer respondents multiple options for completing the survey. Explain how you train surveyors.
 - j) Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
 - k) Submit for review the introductory text used to inform respondents about the purpose of the survey. Tell potential respondents that their answers will not affect their ability to prescribe albiglutide, and that their answers and personal information will be kept confidential and anonymous. All text, including questions and answers, are to be non-promotional in language and tone.
 - l) Clarify in your methodology that respondents are eligible for one wave of the survey only.
 - m) Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant variable, and also in aggregate. Submit all methodology and instruments utilized with your assessments.
 - n) The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating HCPs' knowledge of the risks and safe use associated with albiglutide. The

assessment does not assess HCPs' comprehension of the educational materials. Do not offer respondents an opportunity to read or see any educational materials (e.g., prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

- o) Submit for review the survey instruments (e.g., questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
- p) Ensure the HCP knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials. Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Answer options should include an appropriate number of foils. Ensure each question has an "I don't know" answer option. Randomize the order of the multiple choice responses on each survey.
- q) Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions. Do not allow respondents the opportunity or ability to go back to previous questions in the survey. Explain if and when any education will be offered for incorrect responses.

ATTACHMENTS

Revised REMS Document

Sample of REMS Letters

- REMS Letter for HCP (print version)
- REMS Letter for HCP (email version)
- REMS Letter for Professional Societies (print version)
- REMS Letter for Professional Societies (email version)

Sample of REMS Website

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/s/

RAYMOND S CHIANG

10/25/2013

Comments from OSE in response to submitted albiglutide REMS



BLA 125431

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

GlaxoSmithKline LLC
c/o GlaxoSmith Kline
5 Moore Drive
Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA) dated January 11, 2013, received January 14, 2013, submitted under section 351 of the Public Health Service Act, for albiglutide, 30 mg and 50 mg.

We also refer to your May 15, 2013, correspondence, received May 15, 2013, requesting review of your proposed proprietary name, Tanzeum. We have completed our re-review of the proposed proprietary name and have concluded that it is acceptable. The proposed proprietary name, Tanzeum, will be re-reviewed 90 days prior to BLA action date.

If **any** of the proposed product characteristics as stated in your January 11, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Raymond Chiang at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
08/02/2013



BLA 125431/0

EXTENSION USER FEE GOAL DATE

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA), dated January 11, 2013, and received January 14, 2013, submitted under section 351(a) of the Public Health Service Act for albiglutide injection.

On July 12, 2013, we received your July 12, 2013, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 15, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 27, 2013.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
07/30/2013



BLA 125431/0

MID-CYCLE COMMUNICATION

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for albiglutide solution for injection.

We also refer to the teleconference between representatives of your firm and the FDA on June 26, 2013. The purpose of the teleconference was to provide you with 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 Raymond Chiang, Regulatory Project Manager at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology 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: June 26, 2013, 3:00 – 4:00 PM, EST

Application Number: BLA 125431/0
Product Name: Albiglutide solution for injection
Indication: Type 2 diabetes mellitus
Applicant Name: GlaxoSmithKline LLC

Meeting Chair: Jean-Marc Guettier, M.D.C.M.
Meeting Recorder: Raymond Chiang, MPT, MS, MS

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D.	Director
Raymond Chiang, MPT, MS, MS	Regulatory Project Manager
Patricia Madara, MS	Regulatory Project Manager
Jean-Marc Guettier, M.D.C.M.	Clinical Team Leader
Kaveeta Vasisht, M.D., Pharm.D.	Clinical Reviewer
Mehreen Hai, Ph.D.	Acting Chief, Project Management Staff

Division of Biometrics (DB)

Matt Soukup, Ph.D.	Team Leader, DBVII
Bo Li, Ph.D.	Reviewer, DBVII
Japobrata Choudhury, Ph.D.	Reviewer, DBII

Office of Clinical Pharmacology

Lokesh Jain, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer

Office of Biotechnology Products

Susan Kirshner, Ph.D.	Associate Lab Chief, Laboratory of Immunology
Joao Pedras-Vasconcelos, MS, Ph.D.	Visiting Scientist, Division of Therapeutic Proteins

Office of Compliance

Kalavati Suvarna, Ph.D.	Acting Team Leader, Biotech Manufacturing Assessment Branch
-------------------------	--

Lakshmi Narasimhan, Ph.D.

Microbiologist, Biotech Manufacturing Assessment
Branch

Office of Strategic Programs
Kimberly Taylor, MBA, MPH

Operations Research Analyst

Eastern Research Group

(b) (6)

Independent Assessor

APPLICANT ATTENDEES

Carlo Russo, M.D., SVP and General Manager, Alternative Development Program (ADP)
Rickey Reinhardt, M.D., Ph.D., Head, Clinical, ADP
Sharon Shapowal, R.Ph., Head, Regulatory Affairs, ADP
Fred Yang, Ph.D., Head, Biostatistics and Data Sciences, ADP
Alice Loper, Ph.D., Head, Preclinical Development, ADP
Paul Talierco, Associate Director, CMC Biopharmaceuticals, Global Regulatory Affairs
Michael Maurer, Site Director, Manufacturing Operations, Upper Merion
Curtis Maier, Ph.D., Director, Safety Assessment, Platform Technology & Science
Malcolm Young, Ph.D., Director, Pharmacokinetics, Clinical Platforms & Sciences
Caroline Perry, Head, Clinical Operations, ADP
Jason Mallory, Ph.D., Director, Clinical Development, ADP
Margaret Sowell, M.D., Therapeutic Area Director, Cardiovascular and Metabolic Drugs, Global
Clinical Safety and Pharmacovigilance
June Ye, Ph.D., Manager, Clinical Statistics, Clinical Platforms & Sciences
Timothy Wilson, Ph.D., Director, Statistics & Programming, Clinical Platforms & Sciences
Susan Watts, Ph.D., Director, Therapeutic Groups, Global Regulatory Affairs

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

CHEMISTRY, MANUFACTURING AND CONTROLS

1. Upon review of your justification of specifications for drug substance and drug product for the following common assays: (b) (4)
[Redacted]
2. Your (b) (4)
[Redacted]
3. For your (b) (4) you only set acceptance criteria for the (b) (4) which could allow for the appearance of new (b) (4). Although in your response to our information request dated May 10, 2012, you state that (b) (4) you should still revise the specification to include acceptance criteria for (b) (4).

3.0 INFORMATION REQUESTS

CHEMISTRY, MANUFACTURING AND CONTROLS-MICRO

4. Data submitted in response to question 19 (your amendment dated 14 June 2013) for endotoxin assay show that there is sample matrix interference at the lower dilutions. We are concerned that the Limit of Quantification (LOQ) of the assay, (b) (4) is established as the (b) (4). Please evaluate if the assay sensitivity can be improved.
5. Your response to our information requests (dated June 6, 2013 and June 11, 2013) pertaining to (b) (4). These issues impact the microbial quality of the drug product.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns at this time that require risk management.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Late-Cycle meeting is scheduled for October 17, 2013.

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

/s/

MARY H PARKS
07/11/2013



BLA 125431

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

GlaxoSmithKline LLC
5 Moore Drive
Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA) dated January 11, 2013, received January 14, 2013, submitted under section 351 of the Public Health Service Act, for albiglutide, 30 mg and 50 mg.

We also refer to your January 11, 2013, correspondence, received January 14, 2013, requesting review of your proposed proprietary name, Eperzan. We have completed our review of the proposed proprietary name, Eperzan, and have concluded that it is unacceptable for the following reason:

The proposed proprietary name, Eperzan, is orthographically similar to and shares overlapping product characteristics with the currently marketed product, Epogen (epoetin alfa). The orthographic similarity stems from the similar length and shape (7 vs. 6 letters and 2 down strokes) of the names, and similar appearance of the letters comprising the names when scripted. Each name begins with the letter string 'Ep' and ends with the letter strings 'zan' and 'gen' that appear similar when scripted (down stroked 'z' may look like 'g' and 'an' may look like 'en'). Although Eperzan has two letters in the infix, 'er' compared to the 'o' in Epogen, if 'er' is scripted without much rounding or elongation, the length of the two letters may be similar to that of the letter 'o' (See example below).

Eperzan 50mg subQ once weekly
Epogen 50 units/kg subQ 3 times weekly

Moreover, the pair shares overlapping product characteristics such as dosage form (solution for injection) and route of administration (subcutaneous injection). Additionally, the products share similarity in doses (i.e., 50 mg vs. 50 units), therefore a prescription for "Eperzan 50 mg" could be confused with "Epogen 50 units/kg" if the units of measure are misinterpreted or

the word “units” is not fully written. We have identified post-marketing reports of confusion between products with different units of measure when orthographic similarity exists. As an example, a report from ISMP describes confusion between Lovenox 30 mg and Levemir 30 units. This error occurred despite the differences in units of measurement. In the case of Eperzan and Epogen, the differences in units of measure may not be sufficient to prevent a wrong drug error from occurring and the numerical overlap in the dose may also contribute to medication errors. The differences in frequency of administration (once weekly vs. 3 times weekly) may not provide sufficient differentiation considering the strong orthographic similarity and other common product characteristics.

Your external name evaluation also identified Epogen as a name with potential similarities to Eperzan. However, DSI stated that “Epogen shares an overlapping dosage form/route of administration with EPERZAN, but differs significantly with respect to dosage strength, frequency of administration, and usual dose, thereby significantly minimizing the risk for confusion and error between the names in clinical practice.” However, as stated above, the dose overlaps numerically (50 mg vs. 50 units/kg) and the frequency contains the weekly dosing schedule, thus there is a risk of confusion and error between the two names in the presence of a strong orthographic similarity between the names as described above. Thus, based on the similarity of the names and the shared product characteristics, we conclude that the orthographic similarity and overlapping product characteristics creates a potential for confusion between Eperzan and Epogen that may lead to wrong drug errors.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Raymond Chiang at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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/

CAROL A HOLQUIST
04/12/2013



BLA 125431/0

INADEQUATE STUDY REQUEST

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

We refer to your proposed pediatric study request (PPSR) included in your Biologics License Application (BLA), dated January 11, 2013 and received January 14, 2013, submitted under section 351(a) of the Public Health Service Act for EPERZAN (proposed) (albiglutide).

We have reviewed your PPSR and are unable to issue a Written Request at this time. The albiglutide BLA is still under review and a determination of safe use of albiglutide in adults should be made prior to issuing a Written Request for pediatric studies. Therefore, we recommend that you resubmit your proposed pediatric study request following approval of albiglutide for use in adults.

Clearly mark your submission, **“PROPOSED PEDIATRIC STUDY REQUEST”** in large font, bolded type at the beginning of the cover letter of the submission.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

It should be noted, however, that issuance of this letter does not necessarily mean that there is unexpired exclusivity to which pediatric exclusivity could attach under section 351(m) of the Public Health Service Act (PHS Act). If FDA has not determined whether albiglutide is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for a reference product exclusivity determination with supporting data and information to the Agency.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at 301-796-1940.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
04/09/2013



BLA 125431/0

FILING ISSUES

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA), dated January 11, 2013, and received January 14, 2013, submitted under section 351(a) of the Public Health Service Act for EPERZAN (proposed) (albiglutide).

We also refer to our filing notification letter dated March 13, 2013.

We request that you submit the following information:

CLINICAL/STATISTICAL:

1. Please describe your plan to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio for cardiovascular events is less than 1.3 was not included in the BLA. Please explain whether or not your current plan is to conduct a dedicated postmarketing cardiovascular outcomes trial to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio for cardiovascular events is less than 1.3 as recorded in question #14 in the pre-BLA meeting minutes dated November 15, 2012.

LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues. We request that you resubmit labeling (Microsoft Word format) that addresses these issues within three weeks of the date of this letter. The resubmitted labeling will be used for further labeling discussions.

2. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

3. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission.
4. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.
5. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: **“These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”** In this statement, there should not be a parenthesis around the proprietary trade name.
6. In the HL, the Patient Counseling Information Statement must include the following verbatim statement (without quotation marks):
 - **“See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”**
7. In the Table of Contents (TOC), for section 14.3, the section headings and subheadings in the TOC must match the headings and subheadings in the full prescribing information (FPI).
8. In the TOC, the same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
9. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. Section 6.1, line 98 in the FPI should only include the section heading, not the (b) (4).
10. In the FPI, the Patient Counseling Information must reference any FDA-approved patient labeling, include the type of patient labeling, and use the following statement at the beginning of Section 17:
 - **“See FDA-approved patient labeling (Medication Guide and Instructions for Use)”**

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), Medication Guide, and Instructions for Use. 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), Medication Guide, and Instructions for Use 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.

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

We are not currently planning to hold an advisory committee meeting to discuss this application.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RAYMOND S CHIANG

03/22/2013

Signing on behalf of Dr. Mary Parks, DMEP director



IND 065177

MEETING PRELIMINARY COMMENTS

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
Five Moore Drive, Room 5.5381.5C
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Watts:

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

We also refer to your July 24, 2012, correspondence requesting a Pre-BLA meeting to discuss the submission of the Biologic License Application (BLA) for albiglutide in patients with type 2 diabetes mellitus.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: Wednesday, October 10, 2012, 3:00 – 4:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 065177
Product Name: Albiglutide injection
Indication: Type 2 Diabetes Mellitus
Sponsor: GlaxoSmithKline LLC

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Wednesday, October 10, 2012 between GlaxoSmithKline LLC and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible.

BACKGROUND

IND 065177 for albiglutide injection was submitted on December 15, 2005. Albiglutide is being developed as a once-weekly subcutaneous injection for the treatment of type 2 diabetes mellitus (T2DM) as monotherapy (b) (4). It is a recombinant fusion protein consisting of human GLP-1 genetically fused (b) (4) to human albumin. Albiglutide is an agonist of the GLP-1R and acts on pancreatic β -cells to increase insulin production and augment glucose-dependent insulin secretion.

The sponsor plans to submit a Biologic License Application (BLA) in December 2012. The purpose of this pre-BLA Meeting is to obtain FDA feedback and concurrence prior to submission of the BLA.

PRELIMINARY COMMENTS

Your questions are repeated below, followed by our responses in bold print:

Labeling

1. Clinical studies have evaluated the efficacy of albiglutide as monotherapy and in combination with multiple antidiabetic agents. Specifically, the Phase III clinical program evaluated albiglutide as monotherapy, as add-on to single, dual, and triple oral antidiabetic agents, in combination with insulin glargine, and in patients with renal impairment. Can the Review Team comment on GSK's plans to pursue (b) (4) monotherapy indication, as described, for albiglutide?

FDA Response: The decision regarding the acceptability of the proposed restricted monotherapy indication will be made after review of the data submitted to the BLA. A (b) (4) monotherapy indication was not granted for similar products in the class and information in the background package does not suggest that albiglutide affords a benefit that would warrant such an indication.

2. Data permitting, can FDA comment on the acceptability of the proposed efficacy presentation in the 'Clinical Studies' section of the label, e.g., table plus graphic presentations through the primary endpoint?

Considering that some Phase III trials are ongoing under double-blind conditions through 3 years, can FDA comment whether efficacy data beyond the primary endpoint can be provided in labeling, e.g., ITT-OC through Week 104?

FDA Response: While the tabular and graphic presentation of clinical data through the primary endpoint appears reasonable, a final decision regarding the acceptability of the data to be included in the label will be made after review of the BLA. The Agency has, at times, permitted that data beyond the primary endpoint be included in the product label provided the study design and the data for this endpoint are found to be acceptable after review. In general, we prefer that graphs showing longitudinal data be based on the patients who complete the study to the given time point (i.e., completer population) rather than the intent-to-treat population.

3. Does FDA concur with GSK's plans for disclosure of the results of the (b) (4) in Section 14. Clinical Studies of the prescribing information?

FDA Response: It is unlikely that we would allow inclusion of (b) (4) (b) (4) in the label. We plan to label (b) (4) only after we have reviewed and found the data for the definitive (i.e., final) (b) (4) (b) (4) to be acceptable.

Chemistry, Manufacturing and Controls

4. GSK has implemented the manufacturing changes previously discussed with FDA regarding the change from Process 2 to Process 3. Does FDA agree with the location of comparability information to be presented within the BLA?

FDA Response: Yes, we agree with the proposed location of the comparability information in CTD section 3.2.S.2.6 (Manufacturing development) within the BLA.

5. GSK has developed a (b) (4) in response to the Agency's request (22 Nov 2010 FDA Meeting Minutes of 21 Sep 2010 Type C CMC Meeting; post-meeting comment). GSK will provide in the Briefing Package results that support the conclusion that this test is most suitable for characterization and assessment of comparability, rather than for routine monitoring for release and stability. Based on the information in the Briefing Package, does FDA concur with this GSK proposal to maintain the (b) (4) only for characterization purposes?

FDA Response: No, we do not agree at this time that you limit the use of your (b) (4)

6. GSK proposes some changes in the data presentation and/or future data generation for HPLC, Bioassay, and Clarity:
- A. Does FDA agree to the proposed changes in (b) (4)
 - B. Does FDA agree to the presentation of actual and adjusted bioassay results in the BLA?
 - C. Does FDA agree to the proposed change in the drug product clarity acceptance criteria?

FDA Response:

- A. No, at this time we do not favor your proposed integration strategy for (b) (4)

- B. Yes, we accept the presentation of actual and adjusted bioassay results in the BLA.**

Per ICH Q6B “at the time of submission [of an original application] the manufacturer should have established an appropriately characterized in-house primary Reference Material prepared from lot(s) representative of production and clinical materials...In house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material.” You should submit information on your primary and secondary reference materials in your BLA package.

- C. Yes, we agree with your proposed change in the drug product clarity acceptance criteria to conform to European Pharmacopeial standards.**

- 7. GSK plans to submit comparability protocols in the BLA to outline future planned changes and supportive studies for:** (b) (4)
Does FDA concur with the approach and strategy for these comparability protocols as detailed in the Briefing Package?

FDA Response: The adequacy of the comparability protocols is a review issue. We have only one specific comment at this time. You propose to provide data from (b) (4)

- 8. The albiglutide product is a combination product (biological/device). GSK has proposed the location of the pen injector information within the different modules of the drug product sections of the regulatory dossier. Does FDA concur with GSK’s proposal as described in the Briefing Package?**

FDA Response: Yes, we concur with the proposed location of the pen injector information within the different modules of the drug product sections of the regulatory dossier.

- 9. 21 CFR 601.12 and the guidance for Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (July 1997) allow for reduced reporting when there is a protocol or procedure approved in the application. GSK proposes that the procedures and protocols referenced in this guidance be integrated into the appropriate sections of the regulatory dossier.**

- A. New Working Cell Bank derived from a previously approved Master Cell Bank according to a procedure on file in the approved license application (3.2.S.2.3).**

- B. Replacement of an in-house reference standard or reference panel (or panel member) according to procedures and specifications in an approved application (3.2.S.5).
- C. Extension of the expiration dating period based on real-time data in accordance with a stability protocol in the approved application (3.2.S.7.1 and 3.2.P.8.1).

Does FDA concur with these proposals?

FDA Response: Yes, in accordance with 21 CFR 601.12(5)(e), we concur with your proposal to submit protocols for approval with your licence application for a) New Working Cell Bank derived from a previously approved Master Cell Bank in section 3.2.S.2.3; b) Replacement of an in-house reference standard or reference panel (or panel member) in section 3.2.S.5 and c) Extension of the expiration dating period based on real-time data in accordance with a stability protocol in the approved application in sections 3.2.S.7.1 and 3.2.P.8.1.

10. 21 CFR 610.2 "Requests for samples and protocols; official release," details that the Director, Center for Drug Evaluation and Research, may request samples of any lot of any licensed product together with the protocols showing results of applicable tests. GSK understands the request for official release to be uncommon for specified biologics. GSK does not plan to submit a release protocol based on the aforementioned understanding. Does FDA concur?

FDA Response: Yes, your plan not to submit a lot release protocol is acceptable at this time provided you demonstrate you have well controlled manufacturing process based on principles from ICH Q9 and have a validated process that can consistently produce high quality material that can be further monitored by batch analysis.

11. GSK plans to provide a preliminary manufacturing schedule for both drug substance and drug product sites to support ^{(b) (4)} preparation. ^{(b) (4)}



FDA Response: ^{(b) (4)} ^{(b) (4)} Inspection requirements for the device pen injector combination product will be provided at a later date.

Clinical

12. Based on data from the four drug-drug interaction studies, does FDA concur that no clinically meaningful effects were observed and no dosage adjustment is needed when digoxin, warfarin, oral contraceptives, and statins are co-administered with albiglutide?

FDA Response: This is a review issue and evaluation of dose adjustment will be made at the time of the BLA review.

13. Does FDA concur with GSK's plan to provide the Process 3 pharmacokinetic data from Study GLP114856 in labeling?

FDA Response: This is a review issue and a determination will be made at the time of the BLA review.

14.



(b) (4)



(b) (4)

The post-marketing trial should have an analysis plan that addresses control of type 1 error with respect to interim and final analyses of CV risk that evaluate 1.3.

15. After preliminary review of the calcitonin laboratory data and thyroid events of interest, can the Review Team offer preliminary comment/perspective regarding the data presentation for this event of special interest?

FDA Response: The shell table for thyroid neoplasms provided in the briefing document appears reasonable. In addition, provide a shell table for all adverse events and serious adverse events with columns comparing system organ class terms, preferred terms, number of cases in the albiglutide group, all comparators, placebo, and individual comparators.

Provide adverse events tables comparing albiglutide to liraglutide for events of special interest (i.e., thyroid nodules, thyroid neoplasms, calcitonin levels, pancreatitis, pancreatic enzyme abnormalities, hypersensitivity reactions, liver dysfunction, gastrointestinal adverse events, and incidence of hypoglycemia).

16. Does the Review Team have standardized criteria to apply to adverse events of pancreatitis for the purpose of including events and event rate (incidence) in labeling? For example, does the Review Team recommend that isolated asymptomatic elevations of amylase/lipase be included?

FDA Response: We do not have standardized criteria. Labeling observed imbalances in laboratory parameters, including asymptomatic elevations in pancreatic enzymes (amylase/lipase) may provide valuable information to prescribers and we would recommend that these be included in the label. Decisions regarding which event of pancreatitis will be included in the label will be made after we review the data in the BLA submission. In general, we have asked that sponsors present comparative data that take into account differences in randomization and exposure between groups being contrasted.

17. Albiglutide has not been assessed in studies specifically including hepatically impaired subjects. Given that albiglutide undergoes catabolism by proteolysis, is not metabolized by the liver cytochrome system.

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

FDA Response: This is a review issue and a determination will be made at the time of BLA review.

18. Does FDA agree that the risk management proposal outlined in the Briefing Package identifies the key risks/safety concerns and information gaps and that the strategies proposed to address these concerns are adequate?

FDA Response: Based on the information available at this time, we believe that a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of albiglutide outweigh the risks. Therefore, we encourage you to submit a proposed REMS with your application. A complete review of the REMS, in conjunction with the full clinical review of the BLA, will be necessary to determine that the REMS adequately addresses the safety risks and meets the criteria set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act.

We agree that, should albiglutide be approved, you would be required to conduct a Medullary Thyroid Cancer Case Series Registry as a postmarketing required study under FDAAA. As you indicate in your submission, your proposal to participate in the GLP-1 receptor agonist MTC registry consortium is strongly encouraged.

- 19. Does FDA consider a Medication Guide necessary for albiglutide, as a new GLP-1R agonist, to address safety concerns of medullary thyroid cancer and pancreatitis?**

FDA Response: A Medication Guide (MG) will likely be required for albiglutide to address, at a minimum, the medullary thyroid cancer and pancreatitis safety issues. You should submit a Medication Guide as part of your proposed labeling in accordance with 21 CFR 208.

- 20. Does FDA consider a REMS communication plan necessary for albiglutide, as a new GLP-1R agonist, to address safety concerns of medullary thyroid cancer and pancreatitis?**

FDA Response: Yes, consistent with the approvals of other long-acting GLP-1 receptor agonists, a Communication Plan-only REMS approach appears reasonable at this time. However, a complete review of the REMS, in conjunction with the full clinical review of the BLA will be necessary to determine if the REMS adequately addresses the safety risks.

BLA Administrative Aspects, Content and Format

- 21. GSK plans to include a request for waiver of pediatric studies for children <10 years of age and a request for deferral of pediatric studies for children 10 to <18 years of age in the BLA submission. Does FDA agree that this is appropriate?**

FDA Response: Your plan for a waiver and deferral of pediatric studies is generally acceptable. However, the request requires review of the pediatric study plan by the Pediatric Review Committee (PeRC) and a decision will not be finalized until the time of approval.

When you submit your NDA, a pediatric plan must be submitted which includes protocol synopses of the studies you are planning to conduct. The pediatric plan must contain a timeline for the completion of these studies, including the date the final FDA-agreed upon protocol will be submitted, the date studies will be completed and the date final study reports will be submitted.

You must provide scientific rationale supported by sufficient data to justify each applicable waiver criterion (found in 21 U.S.C. 355c) cited in your request. If you are requesting a waiver based on safety concerns or lack of efficacy in pediatric patients, you must submit proposed labeling which reflects the safety concern and/or lack of efficacy.

22. In the Safety Update Report, GSK proposes to provide the final study reports from the glucose clamp study (Protocol GLP108372) and from the repeat-dose phase of the BE study (i.e., Part 2, Protocol GLP114856) as well as deaths, SAEs, pregnancies, and dropouts due to adverse events from the 3-year Phase III studies. During the BLA review, final Year 3 results from the five ongoing Phase III studies (long-term extensions) will become available from April through August 2013, but are not intended for submission during the review clock. Can the Review Team comment regarding the proposed content and timelines for the Safety Update Report, as detailed in the Briefing Package?

FDA Response: Provide both a cumulative update of the albiglutide program as well as an interim safety update of adverse events after the BLA submission cut-off date with the safety update report. Please ensure that the safety update includes adverse events of interest (thyroid nodules, thyroid neoplasms, calcitonin levels, pancreatitis, hypersensitivity reactions, liver dysfunction, gastrointestinal adverse events and incidence of hypoglycemia and any new immunogenicity findings).

Complete study report for the pivotal bioequivalence study (GLP114856) should be submitted at the time of BLA filing.

23. As FDA has previous experience with this class of drug, can the Review Team comment on the likelihood of an Advisory Committee Meeting for albiglutide especially in the context of the FDAAA 2007 requirements?

FDA Response: The albiglutide drug product is a new molecular entity. At present, you should assume this application be presented before an advisory committee. If during the course of review of the BLA, a decision is made to not convene an advisory committee meeting, we will inform of this change in plans.

24. Masked site/subject identification numbers (IDs) will be generated and used for all data in the eCRFs, narratives, study reports, and summary documents from the five ongoing 3-year Phase III studies included in the BLA, as agreed previously with FDA and described in the Briefing Package. A listing that maps the actual subject, treatment, and site IDs can be provided in a separate document and included in the BLA. Does FDA foresee any review issue with this strategy that GSK's blinding plan has not anticipated?

FDA Response: Please clarify how the processes to protect the blind and integrity of ongoing studies will influence the navigability of the overall application. Subject identification across all submitted materials including but not limited to reports, tables, line listings, eCRFs, narratives and datasets should match to facilitate review. Please clarify how you foresee that the listing that maps the masked IDs to the actual IDs will be used by FDA reviewers.

Please note that these internal GSK processes should not impact the efficiency of communications between FDA and GSK during the review process.

25. For all studies in support of T2DM, GSK proposes to submit electronic case report forms (eCRFs) for deaths, for subjects with SAEs, for pregnancies, and for subjects with AEs resulting in discontinuation. GSK also plans to provide case narratives for deaths, for subjects with AEs resulting in discontinuation, for SAEs, and for specific AEs of special interest. GSK does not plan to submit eCRFs or narratives for subjects from studies of other indications (i.e., heart failure). Does FDA concur?

FDA Response: No, study GHT 112670 (in heart failure) will be discussed individually in your summary of clinical safety and integrated analysis of safety. Provide eCRFs and /or narratives for this study.

26. Datasets for all the individual abiglutide Phase III clinical studies included in the BLA will be provided according to the CDISC SDTM and ADaM guidances. These datasets are submitted in lieu of CRF Tabulations/Patient Profiles. The following should be noted:
- Selected data from early clinical studies in GSK legacy format will be included in the integrated ADaM datasets.
 - Integrated datasets will be produced by aggregation of the individual study ADaM packages. Respective integrated packages are presently not planned to be provided in the BLA submission for the integrated analysis efforts; however, based on the needs of the Review Team, these integrated data can be provided concurrently with the individual study packages or subsequent to the BLA submission.
 - An annotated Blank Case Report Form (blankcrf.pdf), Data Definition File (define.xml), and Supplemental Data Documentation (supplemental.pdf) will be provided for the SDTM datasets.
 - A Data Definition File will accompany the ADaM datasets.

A representative SDTM and ADaM package with Blank Case Report Form and Data Define Files will be provided from one of the individual Phase III clinical studies as a demonstrational submission for FDA consideration - similar to what is outlined in planning steps of the CBER guidance, Submission of Data in CDISC Format to CBER - Process for Planning and Accepting CDISC SDTM and ADaM Formatted Submissions in CBER (Dec 2010). Exceptions to the implementation guidance that GSK is aware of will be described in supporting documentation. In the spirit of transparency, exceptions to the implementation guidance for SDTM and ADaM will be complied and provided for Agency feedback in advance of the BLA submission. Does FDA find the above proposed approach acceptable?

FDA Response: We are unsure about the logic behind the placement of raw legacy data into integrated analysis datasets folder. Please refer to the Study Data Specifications document on correct folder structure when submitting legacy data.

Please submit the integrated dataset package for analysis. Including this integrated dataset (even when large in size) is quite helpful to the review team. For your analysis datasets, please ensure you submit a define.xml file format for the data definitions.

The representative SDTM/ADaM package is not necessary in the final submission unless your intent is for review of this data. We believe that such a test submission was already submitted for evaluation and the results sent back to you.

Additional Comments:

We have the following additional comments regarding the immunogenicity assays submitted on August 17, 2011:

1. **In your various antibody ELISA assays, you use Mean \pm 3SD in order to set acceptance limits for your suitability controls. Please ensure that the low positive quality control for this purpose has a concentration that is close to the limit of detection for the assay to ensure that the assay has a reproducible sensitivity. Your low positive quality control should be designed to produce a signal above the (b) (4) [redacted]. The high positive quality control will ensure that the range of the assay remains consistent and should be used at a (b) (4) [redacted].**
2. **Please provide a plan to monitor stability of the various critical reagents for the immunogenicity assays, including suitability controls.**
3. **In your anti-albumin antibody ELISA assay, your positive control (b) (4) [redacted] (b) (4) [redacted]**
4. **We accept that you delay the validation of your the (b) (4) [redacted] until (b) (4) [redacted]**

Human Factor Validation Study:

5. **Human Factors Validation Study results must be submitted at the time of original BLA submission.**

Chemistry, Manufacturing and Controls:

We remind you that the BLA should contain the following microbiology product quality data and information:

6. **For the CMC Drug Substance section (Section 3.2.S), the BLA should include the following information and data:**

(b) (4)

7. For the CMC Drug Product section of the BLA (Section 3.2.P), validation data summaries to support the (b) (4) should be included. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for (b) (4) Test methods and validation data summaries for the container closure integrity test should be submitted in Section 3.2.P.2.5 of the submission.
8. The study protocols and validation data summaries should be included in Section 3.2.P.3.5 for the following:

(b) (4)

9. We recommend that the

(b) (4)

(b) (4)

Clinical

10. Please ensure that units in the text and tables found in the clinical trial reports, clinical summaries and integrated summaries are based on US units.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 1, 2012, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic and the date of submission is on or after October 1, 2012, the application will be subject to “The Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and “The Program” is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm>

[084159.htm](#). We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

/s/

POOJA DHARIA
10/09/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,177

GlaxoSmithKline
Attention: Sharon Shapowal
Head, Regulatory Affairs, ADP
One Franklin Plaza
200 North 16th Street
Philadelphia, PA 19102

Dear Ms. Shapowal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK716155 (recombinant human GLP-1 human albumin fusion protein).

We also refer to the meeting between representatives of your firm and the FDA on August 12, 2008. This was an End-of-Phase 2 meeting to discuss your Phase 3 plans for albiglutide.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1311.

Sincerely,

{See appended electronic signature page}

John Bishai, Ph.D.
Regulatory Project Manager
Division of Metabolic and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of EOP2 meeting held on August 12, 2008

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: End-of-Phase 2

Application No: IND 65,177

Product Name: Albiglutide (GSK716155) Injection-recombinant human GLP-1 human albumin fusion protein)

Sponsor: GlaxoSmithKline

Meeting Date: August 12, 2008

Meeting Time: 10:30AM

Meeting Format: Face-to-Face

Location: White Oak Campus

Meeting Chair: Mary Parks, M.D.

Meeting Recorder: John Bishai, Ph.D.

Division of Metabolism and Endocrinology (DMEP)

Hylton Joffe, M.D., M.M.Sc.	Diabetes Clinical Team Leader
Dragos Roman, M.D.	Clinical Reviewer
Lisa Yanoff, M.D.	Clinical Reviewer
Somya Verma, M.D.	Clinical Reviewer
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader
John Bishai, Ph.D.	Regulatory Project Manager
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff
Leah Ripper	Associate Director of Regulatory Affairs

Office of Clinical Pharmacology

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Lucun Bi, Ph.D.	Clinical Pharmacology Reviewer
Immo Zdrokewski, Ph.D.	Clinical Pharmacology Reviewer
Ritesh Jain, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics

Todd Sahlroot, Ph.D.	Biometrics Team Leader and Deputy Division Director
Wei Liu Ph.D.	Biometrics Reviewer

Office of New Drug Quality Assessment

Suong Tran, Ph.D.

Pharmaceutical Assessment Lead

Office of Surveillance and Epidemiology

Lanh Green, Pharm.D. MPH

Team Leader

Joselyn Swann, Pharm.D.

Safety Evaluator

EXTERNAL CONSTITUENT ATTENDEES

Carlo Russo, MD

SVP, Cardiovascular Metabolic Medicines Dev & General Manager, ADP

Murray Stewart, DM, FRCP

Head, Clinical Development, ADP

Sharon Shapowal

Head, Regulatory Affairs, ADP

Alice Loper

Head, Preclinical Development, ADP

Fred Yang

Head, Biostat & Data Science, ADP

John Ianacone

Manager, Biopharm

Leonard Olszewski

Director, Analytical Method Development

BACKGROUND:

IND 65,177 for GSK716155, albiglutide, a recombinant human GLP-1 human albumin fusion protein for the treatment of type 2 diabetes mellitus was submitted on December 16, 2005. At the Sponsor's request, an End-of-Phase 2 (EOP2) meeting was granted to discuss the albiglutide development program with a primary focus on the feasibility of conducting a long-term cardiovascular outcomes trial in patients treated with albiglutide. The Sponsor also requested feedback on a number of chemistry, manufacturing, and quality control items.

MEETING OBJECTIVES:

To discuss the Phase 3 clinical development plan.

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's responses provided to the Sponsor on August 8, 2008, follow in bold. A summary of the meeting discussion is italicized.

Nonclinical

Question 1: GSK has conducted numerous nonclinical studies consistent with agency guidance and at the specific recommendation of the review division. For example, and as communicated to GSK in the Agency's letter of March 20, 2007, GSK has completed various general acute and chronic toxicology studies and reproductive toxicology studies (see Section 8 of the briefing document for a summary of results) and has initiated a longer term study in monkeys to assess carcinogenic potential. It is our understanding that no further nonclinical studies are needed to support the submission of the initial BLA. Does FDA agree?

FDA Response: Based on the concern for immuno response reactions at the injection sites of some human subjects, the Division would like clarification on whether histopathology data are available with the species-specific surrogate products which were tested in immunogenicity studies in monkey and mice.

Sponsor Response:

1. *Histopathology data are not available from the immunogenicity studies of mice or monkeys dosed with the species-specific homologue of albiglutide (human GLP-1 fused to murine or monkey albumin).*
2. *The sponsor reports that there is no evidence that the local site reactions in human subjects are associated with a systemic immune response.*

This question and response was not discussed during the EOP2 meeting.

Clinical Pharmacology

Question 2: Are the conducted and proposed clinical pharmacology studies (as described in Section 9) sufficient to support the proposed Phase 3 development plan and BLA submission?

- Would it be acceptable to conduct the clinical pharmacology studies (i.e. interaction studies with digoxin, warfarin, oral contraceptives and simvastatin) in parallel with an ongoing Phase 3 outcomes study?

FDA Response: The Division has the following comments that the Sponsor should consider in addition to what has already been proposed for the clinical pharmacology studies:

- **Generally, the highest therapeutic dose is recommended to be evaluated in drug interaction studies if the safety of the dose is established. In this case, the proposed 60 mg QW dosing has not been studied in earlier studies and its safety is unknown. The Division needs more information on the rationale and the data that support this dosage regimen before the drug interaction studies are initiated.**

Sponsor Response:

1. *In Phase IIb, doses up to 100mg monthly have been explored.*
2. *Based on modeling, the 60mg dose is expected to provide the most favorable efficacy and safety profile.*

3. *From the Phase IIb data, starting doses above 50mg are associated with decreased gastrointestinal (GI) tolerability that may be related to C_{max}.*
4. *Titrating up to 60mg in the insulin study (30-45-60mg) may provide better efficacy without compromising GI tolerability.*
5. *In the clinical pharmacology studies, subjects will receive 3 doses of albiglutide to achieve exposures close to steady state prior to investigating the potential for a drug interaction*

FDA Response: The Division expressed its concerns regarding the lack of safety information for doses above 30 mg in the currently proposed phase 3 program. If the drug product were to be marketed in doses greater than 30 mg (e.g., 45 mg and 60 mg ^{(b) (4)} the division would require a comprehensive safety data for such doses.

- **In the proposed interaction study with warfarin, in addition to pharmacokinetic (PK) exposure data, please assess the pharmacodynamic response of warfarin [i.e. international normalization ratio (INR) parameters, INR_{max}, INR_{tmax}, and INR_{AUC}].**

Sponsor Response: Agreed

- **In the proposed interaction study with the oral contraceptive product, evaluate both C_{max} and AUC.**

Sponsor Response: Agreed

- **In the proposed interaction study with simvastatin, measure both simvastatin and simvastatin acid using the chemical assay.**

Sponsor Response: Agreed

- **In addition to the proposed drug interaction studies, the Division recommends evaluating the impact of albiglutide on other drugs commonly used by patients with type 2 diabetes mellitus.**

Sponsor Response: The Sponsor anticipates this would be addressed within the context of the proposed Phase 3 program.

FDA Response: The Division agrees to the aforementioned.

Other than the comments mentioned above, in general, the proposed clinical pharmacology studies appear to be acceptable based on the information the Sponsor has submitted to date. It is acceptable that the drug interaction studies be conducted in parallel with the ongoing Phase 3 program.

Clinical Development Program – General

Question 3: Dose Selection: Overall, does FDA agree with the dose rationale (as described in Section 11.3) and proposed dose selection for Phase 3?

FDA Response: The Division would like clarification on the basis for selecting the 30 mg once weekly dose for Phase 3 given that the 30 mg every other week dose regimen had a comparable degree of efficacy in the Phase 2 program with potential for a better safety profile.

Sponsor Response:

1. Although the absolute difference in HbA1c is small, the sponsor notes that the half-life of albiglutide is 4 to 6 days, which with every other week dosing results in fluctuations in fasting plasma glucose. The sponsor states that over the long term, 30 mg weekly could be more efficacious than the every other week regimen.
2. At 16 weeks, the percent of subjects reaching goal (<6.5% HbA1c):
 - 30mg weekly, ~30%
 - 30mg every other week, ~15%
3. The Sponsor acknowledges the safety and efficacy of the 30 mg every other week ^{(b) (4)}

(Study GLP111892).

FDA Response: The sponsor's response was acknowledged. The Division stated that it is the sponsor's decision as to which dosing regimen to pursue. As always, with the choice of higher doses and a more frequent dosing regimen there could be greater risk for potential safety issues to emerge as development proceeds.

- Please provide the confidence intervals and p-values for the placebo-corrected change from baseline in HbA1c for all the dose regimens in your Phase 2 trial. Also, clarify the dose of exenatide used in this trial.

Sponsor Response:

1. See data provided

HbA1c - Subgroup by Patient Population
Model Adjusted mean change from baseline vs. PBO
with confidence interval and p-value

	Dyslip	Weekly			Biweekly			Monthly	
		4mg	12mg	30mg	15mg	30mg	50mg	50mg	100mg
All patients	-	0.20 (-0.18, 0.58) 0.3100	-0.25 (-0.63, 0.13) 0.1989	-0.62 (-1.08, -0.23) 0.0027*	-0.22 (-0.62, 0.18) 0.2800	-0.86 (-1.36, -0.17) 0.0048*	-0.88 (-1.38, -0.28) 0.0028*	-0.34 (-0.72, 0.04) 0.0789	-0.89* (-1.38, -0.21) 0.0028*
Met patients	-0.46 (-0.88, -0.07) 0.0222*	-0.05 (-0.52, 0.39) 0.7824	-0.22 (-0.66, 0.23) 0.3401	-0.61 (-1.06, -0.16) 0.0109*	-0.25 (-0.71, 0.22) 0.2951	-0.89* (-1.11, -0.21) 0.0048*	-0.71* (-1.17, -0.28) 0.0021*	-0.33 (-0.77, 0.12) 0.1529	-0.62 (-1.08, -0.16) 0.0091*
D&E patients	-	0.73 (0.08, 1.40) 0.0028*	-0.36 (-1.04, 0.33) 0.3059	-0.68 (-1.42, 0.07) 0.0748	-0.19 (-0.91, 0.52) 0.5957	-0.36 (-1.07, 0.35) 0.3236	-0.32 (-0.98, 0.35) 0.3454	-0.38 (-1.25, 0.28) 0.2572	-0.55 (-1.18, 0.10) 0.0973

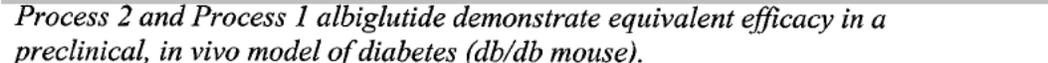
* Statistically significant vs. placebo
D&E: Diet and Exercise
Based on ANCOVA: Change = trt + baseline HbA1c + gender + region



2. The dose of exenatide was per label (5 mcg for 4 weeks followed by up titration to 10 mcg).

- **Process 2 albiglutide that will be used in the Phase 3 program is reportedly less potent than Process 1 albiglutide used in the dose finding Phase 2. Therefore, the Division has concerns that dose selection based on results from the Phase 2 study will not be representative of the doses used in the Phase 3 trials.**

Sponsor Response:

1.  (b) (4)
2. 
3. *Process 2 and Process 1 albiglutide demonstrate equivalent efficacy in a preclinical, in vivo model of diabetes (db/db mouse).*
4. *Dose selection for Phase 3 can be based upon the doses that established efficacy in Phase 2.*

FDA Response: Given the complexity of the albiglutide drug substance and prior experience accumulated with other protein therapeutics within the Agency, the Division continues to be concerned about the immunogenicity of albiglutide; consequently, immunogenicity will be a major focus of the safety review at the time of the NDA submission. The Division strongly

recommends that the Sponsor introduce the to-be-marketed product into phase 3 clinical trials. In response, the Sponsor expressed the difficulty involved in putting the final manufactured product into operation at this stage of development. If the Division's recommendation cannot be followed due to product development logistics, the Sponsor should present in the NDA data that bridge the development product with the commercial product. Due to the complexity of the immunogenicity issue, the Sponsor should not assume that any manufacturing process changes will be viewed strictly from a Chemistry/Manufacturing/Controls (CMC) perspective; the clinical and the CMC reviewers will determine whether the manufacturing changes have the potential to alter the immunogenicity of the product and the extent to which additional clinical data may be necessary. In addition, the Division recommends that data be submitted comparing the impurity profiles of both processes.

- The Division needs more information on the rationale and the data that support the selection of the (b) (4) in Clinical Study GLP108474, since these dose regimens have not been explored during the Phase 2 program.

Sponsor Response: See Question 2.

Question 4: Outcomes trial: The sponsor seeks the perspective of the review team regarding several general questions related to a proposed outcomes study for registration:

- After considering the proposed size, duration, population and design of the trial, and also the assessments of efficacy, adjudication of selected safety events, and proposal to base registration upon a powered interim analysis of efficacy and safety, does the FDA review team have any specific comment(s)?
- Considering that the safety and efficacy profile of albiglutide will be defined in the context of "add-on" to oral hypoglycaemic therapy, and not to placebo per se, does the review team foresee any issue?
- Considering that albiglutide will be "add-on" to a prescribed oral therapy in the outcome trial (i.e. metformin), and that data for albiglutide "add-on" to other oral agents may only be available from the insulin comparison and every other week Phase 3B/4 studies (in which patients enter the studies on a variety of oral diabetic therapies without prespecified number per strata) would the use of albiglutide be limited, initially, by this approach?
- In principal and considering the current state of debate regarding registration of new agents for patients with type 2 diabetes mellitus, could registration be reasonably based upon an approximate 3000 patient years of exposure (to albiglutide), from an interim analysis of the outcomes study, performed when a total of 2500 patients (all patients) have achieved 2 years of treatment?

FDA Response: The Division would like to discuss and explore several issues related to the proposed design of the clinical trial during the face-to-face meeting including the following:

- **the addition of placebo to the control arm of the trial (or at least of a placebo controlled period for part of the trial) to better characterize the treatment effect of albiglutide,**

Sponsor Response:

1. *Treatment effect of albiglutide as add-on therapy may be better characterized against known, approved active comparators rather than placebo.*
2. *Substantial evidence based upon superiority in durability was selected as a more rigorous test of efficacy.*

- **the heterogeneity of the control group (for example some patients will receive sulfonylurea, others will receive a dipeptidyl-peptidase-4 inhibitor, and others may receive a thiazolidinedione or insulin) and whether it is possible with such a design to accurately assess the efficacy and safety of albuglutide,**

Sponsor Response:

1. *Will consider assuring adequate numbers of subjects exposed to each class of agent (balance at entry).*
2. *Example: 200-300 subjects per arm needed to show non-inferiority in HbA1c reduction versus any other class*

- **the open-label design and to better understand why such a study could not be blinded,**

Sponsor Response:

1. *Injection of sham doses (placebo) for 5 years not desired for subjects and may be rejected by Institutional Review Boards.*
2. *We wish to allow physicians to select appropriate therapy matched to the patient, per normal clinical practice.*
3. *In open label design, efficacy bias can be controlled (e.g. HbA1c is an objective measurement; proper blinding of analysis) and agreed safety endpoints will be assessed by a blinded adjudication committee.*
4. *General safety (unsolicited events) may be impacted by bias in reporting.*

- **why not use comparator-adjusted change from baseline in HbA1c as the primary efficacy endpoint for the trial,**

Sponsor Response:

1. *The treat to goal design reflects normal clinical practice, and glycemic benefit in both arms is expected to be approximately equal [imbalance in glycemic control could introduce bias in CV events]*
2. *While absolute reduction in glycemia is important, time to glycemic failure and need for an additional agent is more relevant when assessing long-term efficacy*

where multiple agents can be added. Otherwise, comparator adjusted change from baseline in HbA1c could result in the comparison of effect of one agent to multiple agents.

3. *Will assess change from baseline in HbA1c as secondary endpoint*

- **possible limitations to a potential albiglutide label based on the currently proposed configuration of the Phase 3 program because the above trial will not establish the efficacy and safety of albiglutide in combination with various commonly used antidiabetic medications,**

Sponsor Response:

1. *Would the addition of studies GLP108474 [non-inferiority comparison of albiglutide to insulin glargine] and GLP111892 [non-inferiority comparison of once weekly vs. every other week dosing of albiglutide in combination with metformin] to the Phase 3A program (registration package) address this possible limitation?*

FDA Response: These trials will provide information for these 2 scenarios but there will still not be similar data for other commonly used treatment combinations.

- **the ability of the trial to sufficiently exclude excess cardiovascular risk based on an interim analysis of 2,500 patients who have achieved 2 years of treatment will depend on several factors, including whether a sufficient number of cardiovascular events have accrued during the trial,**

Sponsor Response:

1. *The predicted event rate is 3% per year in the selected population (at interim: 125 events expected to exclude HR 1.8)*
2. *If the event rate does not permit one to statistically exclude excess CV risk at the time of the interim analysis, would this represent a 'refuse to file' or an 'approvability' issue?*

FDA Response: Please see post-meeting note at the end of these minutes.

- **Whether consideration has been given to performing a monotherapy trial and several long-term add-on combination trials (similar in design to current Phase 3 diabetes trials except for long-term controlled extensions), the results from which could be pooled to analyze cardiovascular risk.**

Sponsor Response:

1. *Traditional development has been considered (e.g. expedites product availability, avoids excessive development costs, less complex).*

2. *In context of current medical/scientific discussions, patient complexity and diversity of therapeutic options, an alternative registration path is being explored (+/- supplementary studies).*

- **confirm that the proposed goal of the interim efficacy assessment is superiority of albiglutide vs. control with respect to proportion of therapeutic failures. If the goal is superiority, what is the basis for the choice of alternative hypothesis? Also confirm the expected 2-year failure rates in each treatment group.**

Sponsor Response:

1. *Superiority is the current goal (primary endpoint)*
2. *The 2-year failure rates are based on the data from ADOPT: 5% per year (SU), 3% per year (TZD) and 4% per year (metformin).*
3. *Albiglutide is assumed to be similar (durability of glycemic effect) to TZD*
4. *Assume rate of failure of second line therapy is similar to rate of failure of first line therapy (conservative assumption)*

- **Type 1 errors of 5% (2-sided) may be applied separately for cardiovascular risk and glycemic efficacy. However, additional type 1 error control is recommended for key secondary endpoints and for desired claims in the product label.**

Sponsor Response: *Agreed*

FDA Response: As per the recommendations from the July 1-2, 2008, Endocrinologic and Metabolic advisory committee meeting, please perform prospective, blinded adjudication of cardiovascular events in your phase 3 program. Your phase 3 program should enroll patients who are representative of those who will be treated with your product, if approved (e.g., elderly patients and those with renal impairment in addition to a general type 2 diabetes population).

Question 5: Overall Safety Exposure: At the time of the initial BLA submission GSK anticipates that long-term patient exposures to albiglutide will exceed FDA's 2008 Draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Specifically, approximately 5500 patients would have been exposed to albiglutide for an approximate 3000 patient years.

- Does the size of the clinical trials safety database meet with the Agency's expectation for registration via the route of a proposed outcomes trial?

FDA Response: As mentioned above, the Sponsor will need to explain how the heterogeneity of the anti-diabetic agents permitted in the control group (which have differing effectiveness and safety concerns) permits an accurate assessment of efficacy and safety of albuglutide. For excluding cardiovascular risk, the Division will evaluate the point estimate and upper-bound of the confidence interval for the primary cardiovascular

endpoint. Based on these parameters, the adequacy of the proposed sample size will depend on several factors, including the number of events accrued. If the actual event rate is lower than predicted, it may not be possible to meet the pre-specified non-inferiority margins for excluding cardiovascular risk. Therefore, the Division would like to hear the Sponsor's rationale for not using an event-driven approach for such a trial.

Sponsor Response:

1. See answer to the heterogeneity question (Question bullet No. 2)
2. If event rate high: unable to assess durability of effect and may underestimate long-term CV benefit
3. If event rate low: may take much longer than 5 years to exclude excess CV risk, statistically.
4. Could consider time +/- number of events accrued.

FDA Response: Please see the post meeting note at the end of the minutes.

Clinical Program – Protocol Specific

Question 6: Clinical Study GLP108474 (52-week comparator study versus insulin) (described in Section 11)

With respect to Protocol GLP108474, anticipated to be conducted in Phase 3B/4 such that the data will not likely be available to support the initial BLA registration application, does the Agency agree that:

- The clinical and statistical aspects of the study (which of necessity must be conducted as an open label trial), will include adequate measures to minimize bias on the part of the subjects, observers and analysts of the data such that the trial would be regarded as adequate and well-controlled. Is open label design acceptable?
- The doses selected for this study, i.e. 30 mg weekly, 45 mg weekly, and 60 mg weekly are acceptable?
- The safety monitoring and tolerability endpoints proposed for this study are appropriate?
- The results from this study could be used to support “add on” of albiglutide to other antidiabetic therapies? (N.B. The same question will apply to the study of the every other week regimen, below.)

FDA Response:

- **An open-label design is acceptable. However, the Sponsor will need to ensure that the study is well-executed so that results are not biased towards non-inferiority. For example, the protocol should ensure that the insulin dose is appropriately titrated to maximal effect in all comparator-treated patients. The Sponsor should also justify why only basal insulin is being used as the comparator without pre-meal fast-acting insulin.**

- **See comment regarding doses of 45 mg weekly and 60 mg weekly formulated in answer to Question 1.**
- **The information submitted regarding the safety monitoring and tolerability endpoints is very limited. The Division can provide more specific information when the protocol will be submitted.**

Sponsor Response:

1. *Most T2D patients can commence on once daily insulin; if patients in either arm lose control, they can be “rescued” with prandial insulin.*
2. *A detailed protocol will be submitted*



Sponsor Response:



FDA Response: See response to Question 3. The sponsor should submit a detailed protocol for review. The Division will provide responses to questions that are included in the protocol submission.

Pediatric Plan

Question 8: GSK acknowledges the requirement that all applications submitted under section 351 of the Public Health Service Act (PHSA, 42 U.S.C. 262) for a new active ingredient contain a pediatric assessment unless the applicant has obtained a waiver or deferral. At this time, a pediatric plan is under consideration within GSK with specific focus on a study in children/adolescents ≥ 10 years of age, obese, drug naive and those already receiving metformin monotherapy. Should the data from a future pediatric trial(s) not be available when the BLA for albiglutide use in adults is ready for approval, GSK would likely require a deferral and would apply for such. Pediatric development will be the subject of future discussions with the review team. Is this acceptable?

FDA Response: The proposal for a deferral for children ≥ 10 years of age and a waiver for children < 10 years of age appears to be reasonable. Formal deferral and waiver requests must be included in the NDA. The Division will discuss the Sponsor's request with the Pediatric Review Committee (PeRC) prior to making a final determination.

Sponsor Response: Agreed

Other FDA Comments:

- **All phase 3 clinical trials of albiglutide should include, pancreatitis, and thyroid tumors as adverse events of special interest. Systemic allergic reactions should be evaluated prospectively. As previously indicated, immunogenicity should be evaluated at specified times (e.g 3-month, 6-month, 9-month, 12-month, 18-month and every 6 months thereafter).**

Sponsor Response:

1. *Immunogenicity assessment will be performed at baseline in all subjects, but may not be assessed as frequently as shown on page 111 of briefing document.*
2. *The events of special interest for this class of agents are acknowledged.*

- **We remind you that, if your application will be a BLA, all requirements in 21 CFR Subchapter F – Biologics – that are relevant to Chemistry, Manufacturing, and Controls will apply. For example, as per 21 CFR 610.11, a General Safety test using specific animals will be required as part of your product specification (currently lacking this test).**

Sponsor Response:

1. *While albiglutide would be exempt from GST per 21 CFR §601(2)(c)1, other parts of 600-608 may apply and will be followed for purposes of licensure.*

FDA Response: Although the product is a fusion protein, its intended use as a metabolic hormone (glucagon) will take precedence. Therefore, the product will be accepted in the Center for Drug Evaluation and Research (CDER) as a NDA as opposed to a BLA.

Post Meeting Note:

FDA is finalizing its position regarding whether there should be a requirement for more extensive cardiovascular assessment for new and some already approved drugs developed for the treatment of type 2 diabetes. We will be communicating our decision regarding the need for this more extensive cardiovascular assessment to sponsors of these therapies in the near future. We recommend that you await this communication before finalizing your phase 3 plans.

Linked Applications

Sponsor Name

Drug Name

IND 65177

GLAXOSMITHKLINE

Albigutide / REC HU GLP-1 REC HU
ALBUMIN FUSION PROTEIN

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

/s/

JOHN M BISHAI
10/21/2008

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125431/0

LATE-CYCLE MEETING MINUTES

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for albiglutide solution for injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 13, 2014.

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 Raymond Chiang, Regulatory Project Manager at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier
Director (Acting)
Division of Metabolism and Endocrinology 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: January 13, 2014; 11:00 AM to 12:30 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room Number: 1415
Silver Spring, MD 20903 (teleconference)

Application Number: BLA 125431
Product Name: Albiglutide for injection, for subcutaneous use
Applicant Name: GlaxoSmithKline LLC

Meeting Chair: Ali Mohamadi, M.D.
Meeting Recorder: Raymond Chiang, MPT, MS, MS

FDA ATTENDEES

Office of New Drugs; Office of Drug Evaluation II

Curtis Rosebraugh, M.D., M.P.H. Director, Office of Drug Evaluation II (ODEII)

Office of New Drugs; Office of Drug Evaluation II; Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director (Acting)
Suchitra Balakrishnan, M.D., Ph.D.	Deputy Director for Safety
Ali Mohamadi, M.D.	Clinical Team Leader
Kaveeta Vasisht, M.D., Pharm.D.	Medical Officer
Mehreen Hai, Ph.D.	Safety Regulatory Project Manager
Raymond Chiang, MPT, MS, MS	Regulatory Project Manager

Office of Scientific Investigations

Cynthia Kleppinger, M.D. Medical Officer

Office of Clinical Pharmacology; Division of Clinical Pharmacology II

Lokesh Jain, Ph.D.	Clinical Pharmacology Team Leader
Ritesh Jain, Ph.D.	Clinical Pharmacology Reviewer

Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment; Biotech Manufacturing Assessment Branch

Patricia Hughes, Ph.D.	Team Leader
Bo Chi, Ph.D.	Quality Microbiology Reviewer
Lakshmi Narasimhan, Ph.D.	Quality Microbiology Reviewer

Office of Pharmaceutical Science, Office of Biotechnology Products, Division of Therapeutic Proteins

Susan Kirshner, Ph.D.	Associate Laboratory Chief
Joao Pedras-Vasconcelos, Ph.D.	Quality Reviewer
Arulvathani Arudchandran, Ph.D.	Quality Reviewer
Montserrat Puig, Ph.D.	Quality Reviewer

Office of Biostatistics; Division of Biometrics II

Bradley McEvoy, Ph.D.	Statistical Reviewer
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Office of Biostatistics; Division of Biometrics VII

Mat Soukup, Ph.D.	Lead Mathematical Statistician
Bo Li, Ph.D.	Statistical Reviewer

Office of Surveillance and Epidemiology

Margarita Tossa	Safety Regulatory Project Manager
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Office of Surveillance and Epidemiology; Division of Risk Management

Joyce Weaver, Pharm.D.	Risk Management Analyst
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Office of Surveillance and Epidemiology; Division of Pharmacovigilance I

Debra Ryan, Pharm.D.	Safety Evaluator
----------------------	------------------

Center for Devices and Radiological Health

Keith Marin, MS, MBA, OCN	Regulatory Research Officer
Felicia Binion Williams	Regulatory Research Officer

EASTERN RESEARCH GROUP ATTENDEES

 (b) (6)	Independent Assessor
	Independent Assessor

APPLICANT ATTENDEES

Carlo Russo, M.D.	SVP and General Manager, Alternative Development Program (ADP)
Rickey Reinhardt, M.D., Ph.D.	Head, Clinical, ADP
Sharon Shapowal, R.Ph.	Head, Regulatory Affairs, ADP
Fred Yang, Ph.D.	Head, Biostatistics and Data Sciences, ADP
Alice Loper, Ph.D.	Head, Preclinical Development, ADP
Jason Mallory, Ph.D.	Director, Clinical Development, ADP
Margaret Sowell, M.D.	Therapeutic Area Director, Cardiovascular and Metabolic Drugs, Global Clinical Safety and Pharmacovigilance
Philip Ambery, M.D.	Director, Clinical Development, Cardiovascular and Metabolic Drugs
Curtis Maier, Ph.D.	Director, Safety Assessment, Platform Technology & Science
Vikki Smith	Manager, Biopharm Quality Control
Mike Wilks	Senior Investigator, Product Development, Device Engineering, Platform Technology & Science
Dany Doucet, Ph.D.	Senior Scientific Investigator, Biopharm Product Sciences, Biopharm R&D
Jacek Mozdanowski	Manager, Biopharm Development Analytical Sciences, Biopharm R&D
Amy Ebel	Director, Strategic Labeling, Global Regulatory Affairs
Paul Talierco	Associate Director, CMC Biopharmaceuticals, Global Regulatory Affairs
Susan Watts, Ph.D.	Director, Therapeutic Group, Global Regulatory Affairs

1.0 BACKGROUND

BLA 125431/0 was submitted on January 11, 2013, received on January 14, 2013, for Albiglutide for injection, for subcutaneous use

Proposed indication(s): Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

PDUFA goal date: April 15, 2014

FDA issued a Background Package in preparation for this meeting on January 6, 2014.

2.0 DISCUSSION

1. Introductory Comments
2. Discussion of Substantive Review Issues

Center for Devices and Radiological Health (CDRH)

In BLA 125431, you have provided a risk assessment for the device. The risk assessment addressed the cytotoxicity test. We have no further questions regarding the cytotoxicity data. However, we requested the data for the sensitization and intracutaneous or irritation studies and this was not provided. We need full test studies and protocols for the sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO 10993-10 Irritation or intracutaneous and Sensitization.

Comment sent by CDRH reviewer on January 7, 2014: In lieu of doing the complete biocompatibility testing, the sponsor can address the following:

You have concluded in the risk assessment that “literature study searches conducted on the materials show no potential for cytotoxicity, sensitization, or intracutaneous irritation.” However, you did not provide specific references to support this statement. There is not a significant amount of concern about the potential for irritation to occur since the cytotoxicity test was negative and the polymeric portion of the device is in contact with the patient for such as short time. If you can demonstrate that the polymer has an identical composition to one that has undergone irritation and sensitization testing in the literature and was shown to be negative with cytotoxicity, then there is no to do the testing, but in the absence of these data from the literature, then you should do the testing. The information should be provided in narrative with accompanying references.

GSK response on January 9, 2014: A risk assessment was performed based on ISO-14971, which then led to application of ISO-10993-01. Based on this assessment, biocompatibility data according to ISO-10993-10 tests for irritation and skin sensitisation were not warranted.

As shown in Table 2 of the NAMSA report submitted as Attachment 1 in sequence 0035, the most stringent testing according to USP < 88> Class VI for Polymers, which includes intracutaneous implantation in two species, was performed on the three polymers. Based on these data, the transient skin contact with the hand held pen injector (greater than 400,000 uses in clinical trials), and the fact that drug product does not come in contact with the polymers, the risk assessment concluded no need for further in vivo sensitisation testing.

Discussion: CDRH stated that the risk assessment the sponsor provided is acceptable. However, although the results of intracutaneous implantation studies may be useful to determine whether irritation testing is necessary, it cannot be used as a surrogate for in vivo sensitization testing. The sponsor indicated that the sensitization testing was present in the Drug Master Files (DMF). The sponsor will need to provide the LOA for the DMF and specify specifically where this information can be found.

3. Discussion of Minor Review Issues

CDRH

During the initial review we requested the Material Safety Data Sheets. However, this information was not provided. You have stated that the materials identified within their table are in accordance with Title 21 Code of Federal Regulations, 21 CFR 177. Please provide the material safety data sheets for the materials listed in the tables under the Device Description. This information is needed to assess the safety of your device.

GSK response on January 10, 2014: On 29 Nov 2013, the requested MSDS were provided as Attachments 8-10 (reference: sequence 0042).

Discussion: The MSDS sheets have been provided as requested. CDRH has no additional comments at this time.

Office of Compliance, Office of Manufacturing and Product Quality, Division of Good Manufacturing Practice Assessment; Biotech Manufacturing Assessment Branch (CMC)

[Redacted] (b) (4)

- [Redacted] (b) (4)
- [Redacted]
- [Redacted]
- [Redacted]

(b) (4)

(b) (4)

In amendment 36, you recently submitted new specifications and justifications of specifications for drug substance (attachments 1 and 2) and drug product (attachments 3 and 4) but failed to update the appropriate sections of the eCTD. Please update Sections 3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1, and 3.2.P.5.6 as appropriate.

Comment sent by CMC reviewer on January 7, 2014: The reviewer commented that this minor comment has been addressed.

Discussion: No Comments.

If you would like an (b) (4) dating period for DS and DP, please provide (b) (4) stability update for process 3 registration lots of drug substance and drug product to the file.

Comment sent by CMC reviewer on January 7, 2014: The reviewer commented that this minor comment has been addressed.

Discussion: No Comments.

4. REMS or Other Risk Management Actions

We conducted a preliminary review of the REMS you submitted, and we sent you comments October 25, 2013. We remind you that the language in the REMS materials must be consistent with the final agreed-upon labeling.

Discussion: GSK acknowledged the response submitted in Sequence No. 0045 (18Dec2013) to FDA's REMS comments dated 25Oct2013. FDA indicated that further changes to REMS materials will likely be required to ensure that the REMS is consistent with the final labeling.

5. Postmarketing Requirements/Postmarketing Commitments

Clinical Postmarketing Requirements

- A randomized, double-blind, placebo-controlled trial evaluating the effect of albiglutide on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with albiglutide to that observed in the placebo group is less than 1.3.

GSK response on January 10, 2014: GSK's proposal for this study synopsis with questions for the Review Team was sent by email on 05Dec2013. Does the Review Team have feedback for GSK, most importantly regarding the acceptability of the co-primary endpoints and the large simple study design and conduct? Feedback is critical at this point for GSK to proceed with planning the implementation of this study, including timelines.

Discussion: The CVOT proposal is currently under review and comments are pending internal discussions.

-  (b) (4)

Discussion: No Comments.

- A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of albiglutide for the treatment of type 2 diabetes in pediatric patients ages 10 to < 18 years.

GSK response on January 10, 2014: The Review Team has specified two PREA PMRs: a Phase 1 PK study and a randomized safety and efficacy study in T2DM patients 10 to <18 years of age. The PPSR provided in the original BLA, m1.9.4 described GSK's plans to conduct a single pediatric study, with Part A (single-dose PK analysis in sequential cohorts of 14 to <18 year olds and then 10 to <14 year olds) conducted to inform the subsequent conduct of Part B (16-week, randomized, double-blind, placebo-controlled, repeat-dose safety and efficacy study followed by a 36 week open-label extension). Single-dose exposure and tolerability data from Part A will be analyzed to allow for appropriate dose-adjustment (if necessary) prior to progression to repeat-dose Part B, to

ensure exposures are maintained within a range previously demonstrated to be safe and well-tolerated and pharmacologically relevant.

GSK would like to proceed with a single multi-part study and thus requests that FDA write our PMR accordingly.

Furthermore, does the Review Team need any further pediatric plan submitted by GSK in advance of approval, aside from agreement on the PREA PMR?

Discussion: The review team is meeting with FDA's Pediatric Review Committee (PERC) on January 25, 2014 and will provide additional comments regarding the pediatric plan after this internal meeting. GSK noted that the pediatric study has already been agreed with EMA; however, FDA noted that their requirements may be different. FDA confirmed that GSK does not need to submit any further pediatric information prior to BLA approval.

- Additional postmarketing requirements (PMRs)/postmarketing commitments (PMCs) are still under discussion within the Agency. We will notify you of any additional PMRs or PMCs later in the review cycle. Please note that the Pediatric PMRs for albiglutide still need to be cleared by our internal Pediatric Committee.

GSK response on January 10, 2014: With respect to the remaining review period, can the Review Team provide some guidance relative to the timelines for communication of any additional PMRs or PMCs?

Discussion: Primary Reviews have been completed and additional PMRs and PMCs are pending secondary and tertiary reviews of the application.

CMC Postmarketing Commitments

- To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.

GSK response on January 10, 2014: GSK acknowledges that this will be a post marketing commitment.

Discussion: No Comments.

- To develop, validate, and implement an FcRN binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.

GSK response on January 10, 2014: GSK acknowledges that this will be a post marketing commitment.

Discussion: No Comments.

CMC/Micro Postmarketing Commitments

- Develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in the relevant containers.

GSK response on January 10, 2014: GSK would like to propose alternate wording for this PMC: (b) (4)

[REDACTED]

Discussion: FDA requested that the original language in the PMC for the development a reliable endotoxin test be retained because a reliable detection method may require a new test and not just optimization of the current method. The sponsor agreed.

FDA stated that these commitments are being requested from all sponsors with similar endotoxin masking issues, as seen for certain formulations. FDA indicated that another type of test may have to be developed to overcome the endotoxin masking observed using the LAL method. For example, reports have been published indicating good results with the EndoLISA method.

- Conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product.

GSK response on January 10, 2014: Low Endotoxin Recovery (LER) proves to be a very challenging issue. Studies have been initiated and GSK will continue to develop an optimized assay and investigate the mechanism of low endotoxin recovery. GSK would be prepared to provide progress updates.

Discussion: GSK affirmed plans to pursue the best method and noted plans for confirmatory pyrogenicity testing. FDA requested that GSK provide a plan with deliverables and proposed postapproval timelines for updates for endotoxin assay investigations.

6. Major Labeling Issues

GSK response on January 10, 2014: GSK can provide an update during the LCM teleconference on our consideration of the outstanding labeling comments that were not addressed in GSK's USPI draft version provided in my email from 08 Nov (submitted as Sequence No. 0039), i.e., safety labeling regarding hypersensitivity (FDA text in Sections 4.2 and 5.6), hepatocellular injury (FDA text in Section 6.1), and appendicitis (FDA text in Section 6.1). (The most recent albiglutide draft label was emailed to GSK on January 10, 2014)

Discussion: The review team requested written communication from the sponsor regarding labeling issues.

7. Review Plans

8. Wrap-up and Action Items

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

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/s/

JEAN-MARC P GUETTIER
01/30/2014



BLA 125431/0

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

GlaxoSmithKline LLC
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
5 Moore Drive, Room 5.5381.5C
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for albiglutide solution for injection.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 13, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director (Acting)
Division of Metabolism & Endocrinology 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: January 13, 2014; 11:00 AM to 12:30 PM EST

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room Number: 1415
Silver Spring, MD 20903

Application Number: BLA 125431

Product Name: Albiglutide for injection, for subcutaneous use

Indication: Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Sponsor/Applicant Name: GlaxoSmithKline LLC

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

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

The following substantive review issue, from Center of Devices and Radiological Health (CDRH), has been identified to date:

In BLA 125431, you have provided a risk assessment for the device. The risk assessment addressed the cytotoxicity test. We have no further questions regarding the cytotoxicity data. However, we requested the data for the sensitization and intracutaneous or irritation studies and this was not provided. We need full test studies and protocols for the sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO 10993-10 Irritation or intracutaneous and Sensitization.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS/RISK MANAGEMENT ACTIONS HAVE BEEN IDENTIFIED

We conducted a preliminary review of the REMS you submitted, and we sent you comments October 25, 2013. We acknowledge receipt of your revised REMS (eCTD sequence 45) in response to our comments. We remind you that the language in the REMS materials must be consistent with the final agreed-upon labeling.

LCM AGENDA

1. Introductory Comments – (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues
The following issue will be introduced by FDA and followed by a discussion:
CDRH

In BLA 125431, you have provided a risk assessment for the device. The risk assessment addressed the cytotoxicity test. We have no further questions regarding the cytotoxicity data. However, we requested the data for the sensitization and intracutaneous or irritation studies and this was not provided. We need full test studies and protocols for the sensitization and intracutaneous studies. In order for us to complete our review of this device, the following information is needed: complete biocompatibility data for the following test using the complete final finished product: ISO 10993-10 Irritation or intracutaneous and Sensitization.

3. Discussion of Minor Review Issues
CDRH

During the initial review we requested the Material Safety Data Sheets. However, this information was not provided. You have stated that the materials identified within their table are in accordance with Title 21 Code of Federal Regulations, 21 CFR 177. Please provide the material safety data sheets for the materials listed in the tables under the Device Description. This information is needed to assess the safety of your device.

CMC

•



- In amendment 36, you recently submitted new specifications and justifications of specifications for drug substance (attachments 1 and 2) and drug product (attachments 3 and 4) but failed to update the appropriate sections of the eCTD. Please update Sections 3.2.S.4.1, 3.2.S.4.5, 3.2.P.5.1, and 3.2.P.5.6 as appropriate.
- If you would like an (b) (4) dating period for DS and DP, please provide (b) (4) stability update for process 3 registration lots of drug substance and drug product to the file.

4. REMS or Other Risk Management Actions

We conducted a preliminary review of the REMS you submitted, and we sent you comments October 25, 2013. We remind you that the language in the REMS materials must be consistent with the final agreed-upon labeling.

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Clinical Postmarketing Requirements

- A randomized, double-blind, placebo-controlled trial evaluating the effect of albiglutide on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke,

cardiovascular death) observed with albiglutide to that observed in the placebo group is less than 1.3.

-  (b) (4)
- A randomized and controlled pediatric study under PREA to evaluate the efficacy and safety of albiglutide for the treatment of type 2 diabetes in pediatric patients ages 10 to < 18 years.

Additional postmarketing requirements (PMRs)/postmarketing commitments (PMCs) are still under discussion within the Agency. We will notify you of any additional PMRs or PMCs later in the review cycle. Please note that the Pediatric PMRs for albiglutide still need to be cleared by our internal Pediatric Committee.

CMC Postmarketing Commitments

- To develop, validate and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.
- To develop, validate, and implement an FcRN binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.

-  (b) (4)
-

CMC/Micro Postmarketing Commitments

- Develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in the relevant containers.
- Conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product.

6. Major labeling issues

7. Review Plans

8. Wrap-up and Action Items

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

/s/

JEAN-MARC P GUETTIER
01/06/2014