CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022271Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **022271**

Trade Name **Nesina**

Generic Name **Alogliptin**

Applicant Name **Takeda Pharmaceuticals U.S.A., Inc.**

Approval Date, If Known **January 25, 2013**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Not specified

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **n/a**

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **n/a**

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Richard Whitehead
Title: Regulatory Project Manager
Date: 1/24/13

Name of Office/Division Director signing form: Mary Parks, MD
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

RICHARD E WHITEHEAD
01/29/2013

MARY H PARKS
01/29/2013

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

NDA/BLA#: 22-271 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Metabolism and Endocrinology Products PDUFA Goal Date: 10/27/2008 Stamp Date: 12/27/2007

Proprietary Name: TBD

Established/Generic Name: alogliptin

Dosage Form: Tablets

Applicant/Sponsor: Takeda Global Research & Development Center

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

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

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

Indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (type 2 diabetes)

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∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	9 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

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

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

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

Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

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

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

∆ Formulation failed:

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

☒ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	10 yr. __ mo.	(b) (4) yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): TBD						

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

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

Attachment A

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

Indication #2: _____

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

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

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

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

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

∆ Formulation failed:

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

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

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

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

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

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

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

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

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

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

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

(Revised: 6/2008)

Request for Partial Waiver and Partial Deferral of Pediatric Studies
Division of Metabolism and Endocrinology Products

NDA: 22-271
Drug Name: aloglipin tablets
Sponsor: Takeda Global Research & Development Center
Indication: Treatment of type 2 diabetes

Background:
NDA 22-271 for alogliptin tablets was submitted for review on December 27, 2007. Alogliptin is a dipeptidyl-peptidase IV (DPP-IV) inhibitor. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (type 2 diabetes).

Request:
In the original NDA submission on December 27, 2007, the sponsor submitted a request for partial waiver of pediatric studies for ages 0-9 years and a request for a partial deferral of pediatric studies for 10 years of age and older. The sponsor submitted a Pediatric Plan for the deferred studies on May 7, 2008.

Justification:
The Division agrees with the sponsor's request for a waiver of pediatric studies for ages 0-9 years because there are too few children to be studied in this age group with type 2 diabetes mellitus.

The Division agrees with the sponsor's request for a deferral of pediatric studies for ages 10- (b)(4) years because of the need to characterize the safety and efficacy of alogliptin more fully in the adult population prior to conducting studies in pediatric subjects.

The above approach is consistent with the Division's contemporary approach to other drugs developed for the treatment of type 2 diabetes.

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

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 /s/
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Julie Marchick
5/27/2009 01:10:59 PM
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1.3.3 Debarment Certification

Certification Statement as requested by the Generic Drug Enforcement Act of 1992:

This certification is provided for New Drug Application (NDA 22-271, alogliptin tablet). Takeda Global Research & Development Center, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

14-JULY-2011

Jeffrey Soderquist
Vice President, Quality Assurance
Takeda Global Research and Development Center, Inc.

Date

1.3.3 DEBARMENT CERTIFICATION

Certification Statement as requested by the Generic Drug Enforcement Act of 1992:

This certification statement is provided for New Drug Application (NDA 22-271, alogliptin) and is provided in compliance with the Generic Drug Enforcement Act of 1992. Takeda Global Research & Development Center, Inc. hereby certifies it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

20 Nov. 2007

Qais Mekki, MD, PhD
Vice President, Clinical Sciences
Takeda Global Research & Development Center, Inc.

Date

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs
Date: Friday, January 25, 2013 11:52:00 AM
Attachments: Kazano- PI final.doc
Nesina-PI final.doc
Oseni-PI final.doc

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 25, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Friday, January 25, 2013 11:32 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs

Dear Rich,
We have received this email. We are in agreement with these as the final versions with one exception. We noticed there was a formatting issue we had with Table 3 only in the Oseni label. Therefore, we had to extend the row in order for the AE of "upper respiratory tract infection" to be fully visible. I have made that correction and have reattached this label to you. I am also reattaching the other package inserts with no changes as you have sent them to us.
Please let me know if you need anything further.
Kind regards,
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 25, 2013 8:44 AM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 11:51 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271/22426/203414 alogliptin: draft labeling
Importance: High

Dear Rich,
Please find Takeda's edits to the alogliptin product package inserts attached. Please let us know if you need anything further.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M (b) (6)
F 224-554-7870
sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Wednesday, January 23, 2013 3:30 PM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271/22426/203414 alogliptin: draft labeling

Sandy,

Please find attached our next round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical. We ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels. The MedGuides are not being provided at this time.

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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. Because of the tight timelines was ask the you complete your review and return comments **by noon Thursday, January 24th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

###
The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and is the property of Takeda. Unauthorized use, disclosure, or copying of this communication, or any part thereof, is strictly prohibited and may be unlawful. If you received this communication in error, please notify me immediately by return e-mail and destroy this communication and all copies thereof, including all attachments.

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/s/

RICHARD E WHITEHEAD
01/25/2013

From:	Whitehead, Richard
To:	"Cosner, Sandra (TGRD)"
Cc:	Barnes-Glait, Diane (TGRD)
Subject:	NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft MedGuides
Date:	Friday, January 25, 2013 9:43:00 AM
Attachments:	Nesina- MedGuide final.doc Oseni-MedGuide final.doc Kazano MedGuide final.doc

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Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) Medication Guides (MG) and we accept all revisions to the MGs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 2:22 PM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: Nesina, Oseni, Kazano MedGuides Review
Importance: High

Hello Rich,
Please see Takeda's comments in the attached medication guides for the alogliptin products. We accepted all the Agency's comments with the exception of one comment in the OSENI (alo/pio) Medication Guide.

Please let us know if you have any questions.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
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U.S.A.
T 224-554-1957
M (b) (6)

F 224-554-7870
sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, January 24, 2013 10:47 AM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: Nesina, Oseni, Kazano MedGuides Review

Sandy,

I am forwarding the next round of comments from Patient Labeling for the Nesina, Oseni, and Kazano MedGuides. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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. Because of the tight timelines was ask the you complete your review and return comments by **COB today (January 24)** .

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/25/2013

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271 Nesina; NDA22426 Oseni; NDA203414 Kazano: draft PIs
Date: Friday, January 25, 2013 9:43:00 AM
Attachments: Nesina-PI_final.doc
Oseni-PI_final.doc
Kazano- PI_final.doc

Dear Sandy,

We have reviewed the NDA 22271 Nesina (alogliptin), NDA 022426 Oseni (alogliptin and pioglitazone) and NDA 203414 Kazano (alogliptin and metformin) prescribing information (PI) and we accept all revisions to the PIs dated January 24, 2013. I am attaching a clean copy of these agreed upon documents. Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, January 24, 2013 11:51 AM
To: Whitehead, Richard
Cc: Barnes-Glait, Diane (TGRD)
Subject: RE: NDA22271/22426/203414 alogliptin: draft labeling
Importance: High

Dear Rich,
Please find Takeda's edits to the alogliptin product package inserts attached. Please let us know if you need anything further.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M (b) (6)
F 224-554-7870
sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Wednesday, January 23, 2013 3:30 PM
To: Cosner, Sandra (TGRD)
Cc: Barnes-Glait, Diane (TGRD)
Subject: NDA22271/22426/203414 alogliptin: draft labeling

Sandy,

Please find attached our next round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical. We ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels. The MedGuides are not being provided at this time.

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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. Because of the tight timelines was ask the you complete your review and return comments **by noon Thursday, January 24th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/25/2013

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject: RE: NDA 22271 Disclosure
Date: Wednesday, January 16, 2013 9:59:00 AM

Sandy,

Please see the response from the review team to your inquiry. Let me know if you have any questions.

At present, FDA continues to have internal discussions on this matter and many senior staff including disclosure staff are aware of the impact of any such decision on NDA 22271. Please note that should NDA 22271 be approved, reviews are not posted until approximately 6 weeks after the approval date. Takeda will be informed of what information pertaining to EXAMINE will be posted in advance of this occurring.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Tuesday, January 15, 2013 1:25 PM
To: Whitehead, Richard
Subject: NDA 22271 Disclosure

Dear Rich,

As we are nearing the PDUFA date for the alogliptin products, Takeda would like to follow up with the Division to see if a determination has been made on how the FDA intends to handle review documents posted on the FDA's website containing ongoing cardiovascular outcome trial data following product approval. Takeda had previous discussions with the Agency at the End of Review meeting held on June 29, 2012. At this meeting, Takeda inquired as to what specific information the Agency would make public with regard to the ongoing CV trial (Study 402) in order to be prepared to manage communications with investigative sites. Should alogliptin be approved, Takeda is preparing for how to answer questions from DMC, current investigators, general public regarding the data publically available from this ongoing trial; therefore, any insights into the level of information that could be included in an SBA would be greatly appreciated.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
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www.tgrd.com

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/s/

RICHARD E WHITEHEAD
01/23/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com); Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject: RE: Nesina, Oseni and Kazano PMR- request for clarification
Date: Wednesday, January 16, 2013 12:30:00 PM

Sandy,

See responses to your inquiries below in red. Let me know if you have any additional questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

---

From: Cosner, Sandra (TGRD)
Sent: Tuesday, January 15, 2013 10:09 AM
To: 'Whitehead, Richard'
Cc: Barnes-Glait, Diane (TGRD)
Subject: Nesina, Oseni and Kazano PMR- request for clarification

Dear Rich,

Thank you very much for providing the postmarketing requirements (PMR) for the alogliptin family of products yesterday following the teleconference. Takeda has reviewed the requests and has a couple points of clarification for the Agency in order to develop the most accurate timelines:

For Nesina NDA22271
Regarding PMR #1:

The current pediatric protocol for the ongoing PK study SYR-322_104 [Amendment #8 submitted to IND 69707 Mar 22, 2012 (S/N 672)] specifies different age ranges for the two groups being examined. The protocol specifies that Group 1 is 10 to 13 year olds, inclusive and Group 2 is 14 to 17 year olds, inclusive. Further, the protocol specifies that at least 6 subjects (25%) will be in Group 1 and 18 subjects (75%) will be randomized in Group 2. In addition to submitting all versions of the protocol to the Agency, this study design has been agreed with the Paediatric Committee (PDCO) at the European Medicines Agency. Therefore, Takeda would propose that the age requirements in the PMR match the protocol as currently specified (i.e. 25% of subjects 10 to 13 year olds, inclusive and 75% of subjects 14 to 17 year olds, inclusive). Is this acceptable to the Agency? The Agency finds this acceptable.

Regarding PMR #4:

Takeda would like to seek guidance on the content of the protocol for the enhanced

pharmacovigilance (PV) program. Takeda would propose that this protocol would not conform to a typical clinical study protocol, but would contain the following information:

1. Criteria for collection of information
2. Process for collection of information, including data collection forms
3. Requirement for reporting findings on an annual basis, including format of the analysis

Will this type of information satisfy the Agency's requirement for a protocol to address enhanced pharmacovigilance? If not, can the Agency provide Takeda with additional information as to the requirements for a protocol for an enhanced PV program? The Agency is OK with your proposal; however, in addition to the annual report, expedited reporting of these events is required:

> Expedited reporting to FDA of all initial and follow-up reports of hepatic abnormalities, fatal pancreatitis and hemorrhagic/necrotizing pancreatitis with a serious outcome, and severe hypersensitivity reactions.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
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sandra.cosner@takeda.com
www.tgrd.com

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/s/

RICHARD E WHITEHEAD
01/23/2013

From:	Whitehead, Richard
To:	Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc:	Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject:	Nesina, Oseni, Kazano MedGuides Review
Date:	Friday, January 18, 2013 3:12:00 PM
Attachments:	marked --alogliptin-metformin (Kazano) 203414 DMPP MG Jan 2013.doc marked-alogliptin-pioglitazone (Oseni) 22426 DMPP MG Jan 2013 .doc alogliptin (Nesina) 22271 DMPP MG Jan 2013 (marked).doc

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Sandy,

I am forwarding the first round of comments from Patient Labeling for the Nesina, Oseni, and Kazano MedGuides. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please note that not all reviewers have looked at this yet so more comments may come on Tuesday, however at this point they should not be extensive (but as always that could change).

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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. Because of the tight timelines was ask the you complete your review and return comments by **7AM Tuesday, January 22nd** .

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

RICHARD E WHITEHEAD
01/18/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc: Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject: Nesina, Oseni, and Kazano: PMR
Date: Monday, January 14, 2013 2:20:00 PM
Attachments: Postmarketing Requirements for Nesina1102013.doc

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Dear Sandy,

As discussed at today's telephone conference I am forwarding a copy of Postmarketing requirements for Nesina, Oseni, and Kazano should your product(s) be approved. We request that you provide dates for study completion, final reports, etc., as described in the in the document. Email all requested information to me within two days of receipt of this notification. You do not have to submit these officially to the applications. Please confirm receipt of this email.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/14/2013

From:	Whitehead, Richard
To:	Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc:	Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject:	NDA22271 and NDA203414: Revised Carton and Container Labeling
Date:	Thursday, January 10, 2013 7:07:00 AM

Dear Sandy,

We have reviewed the revised carton and container labeling for Nesina (alogliptin) and Kazano (alogliptin and metformin) submitted on January 9, 2013 and the addition of the statement "Dispense with Medication Guide" is acceptable for both Nesina and Kazano. However, upon further evaluation of the carton and container labeling, we have the following recommendations:

Nesina:

- If the blister card packaging is not child-resistant, we recommend adding the statement "Enclosed Packages Are Not Child Resistant. Keep out of reach of children" to the professional sample blister card carton labeling, so that it is consistent with Oseni (alogliptin and pioglitazone).
- On the Principal Display Panel of the professional sample bottle carton labeling, add the statement "Contains 4 patient bottle samples of 7 tablets each," so that it is consistent with Oseni (alogliptin and pioglitazone).
- On the Principal Display Panel of the professional sample blister card carton labeling, add the statement "Contains 4 patient blister samples of 7 tablets each," so that it is consistent with Oseni (alogliptin and pioglitazone).

Kazano

- If the blister card packaging is not child-resistant, we recommend adding the statement "Package Not Child Resistant. Keep out of reach of children" to the professional sample blister card container label, so that it is consistent with Oseni (alogliptin and pioglitazone).
- If the blister card packaging is not child-resistant, we recommend adding the statement "Enclosed Packages Are Not Child Resistant. Keep out of reach of children" to the professional sample blister card carton labeling, so that it is consistent with Oseni (alogliptin and pioglitazone).

Let me know if you have any questions and please confirm receipt of this notification.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/10/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Tuesday, January 08, 2013 4:48:00 PM

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response Wednesday, January 9th. Let me know if you have any questions and please confirm receipt of this email notification.

"In your 2nd resubmission the following table was provided for EXAMINE which led FDA to request the incidence of transaminase elevations be summarized for pooled Phase 2/3 trials.

Table 7 Number and Percentage of Subjects With Markedly Abnormal ALT Values (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result			
	Baseline		Post-Baseline	
Parameter (Criterion)	Placebo N=1466	Alogliptin N=1467	Placebo N=1372	Alogliptin N=1387
ALT (>20×ULN)	0	0	0	0
ALT (>10×ULN)	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT (>8×ULN)	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT (>5×ULN)	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT (>3×ULN)	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)
>3×ULN and total bilirubin >2.0 mg/dL	0	0	0	0
>3×ULN and total bilirubin >2×ULN	0	0	0	0

Source: Appendix 8, Table 4.
Note: The Baseline visit window includes all results obtained on or before the date of randomization.

When we compare Table 7 to the updated table provided in Takeda's 1/7/13 response in email below and pasted here, there are 4 patients on alogliptin w/ ALT > 10xULN in the 'during treatment' column but 5 patients in Table 7 w/ ALT > 10xULN in the post-baseline column. Please explain this discrepancy of one patient."

Number (%) of Subjects With ≥1 Marked Abnormal Result						
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389
ALT >3×ULN and total bilirubin >2×ULN	0	0	1 (0.04)	1 (0.04)	0	1 (0.04)
ALT >20×ULN	0	0	1 (0.04)	0	0	0
ALT >10×ULN	1 (0.04)	2 (0.08)	2 (0.08)	4 (0.17)	0	1 (0.04)
ALT >5×ULN	2 (0.08)	2 (0.08)	12 (0.51)	19 (0.80)	2 (0.08)	5 (0.21)
ALT >3×ULN	10 (0.42)	14 (0.59)	32 (1.35)	44 (1.84)	8 (0.34)	12 (0.50)

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, January 07, 2013 1:35 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request

Hello Rich,
Please see Takeda's response to FDA's Jan. 4 request in the attached.
I will also submit this as a formal submission to the NDA's, hopefully by the end of today.
Please let me know if you need anything else.
Kind regards,
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/08/2013

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Information Request
Date: Monday, January 07, 2013 8:54:00 AM

Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. We ask that you provide your response by noon, today. Let me know if you have any questions and please confirm receipt of this email notification.

Please explain how you were able to determine that subject 8413-006/402 was assigned to placebo and yet state that this "case currently remains blinded as this is an ongoing study in the safety database". Did you not have to unblind the case to determine treatment assignment?

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Sunday, January 06, 2013 10:11 PM
To: Whitehead, Richard
Cc: Hai, Mehreen
Subject: RE: NDA22271 alogliptin: Jan. 4 Information Request

Dear Rich,

During our evaluation of FDA's latest information request from Friday, Jan. 4 for an update of Table 3f (Markedly abnormal values for hepatic parameters of Study 402), Takeda re-ran the Table with a new database cut (with 6 months of additional data) and has unfortunately learned of an incorrect treatment code on the case of interest in Study 402; subject 8413-006/402 (TPG2012A01058) that was provided to FDA in the July 2012 NDA resubmission. Takeda had inadvertently assigned this case to the alogliptin 25 mg treatment code and subsequently upon this latest review learned that this subject was in fact on placebo.

We would like to reassure the Agency that the statistical tables and outputs from the clinical database are accurate. In addition, the safety database is accurate and this case currently remains blinded as this is an ongoing study in the safety database. This error was in part due to the fact

that this subject was a late breaker case that occurred following the database cut off and that the table in 2.7.4 was manually generated. Because this error was discovered, the team is putting extra effort in QCing all the data in all manually generated hepatic tables from the NDA resubmission (i.e., Tables 3c, 3d and 3i) to confirm these are accurate. The team is also re-checking all current data, randomization codes, and conducting QC checks against previous and current database cut offs. Takeda apologizes and regrets very much that this error has occurred. We understand this case was of specific interest to both Takeda and FDA and we wanted to notify you as soon as we had confirmed this error. Through our investigation, we are ensuring that no other such mis-assignments exist. The case will be properly reflected in our submission that we will be sending to you by the end of the day tomorrow (Jan 7) as per the data you requested last week, at which time the quality control of the other tables will have been completed as well.

We understand the Agency is meeting Monday, January 7 for the second round of labeling comments and potentially later in the week for the end-of-review wrap-up meeting. If the Division has any concerns or would like any additional clarification on this issue, Takeda would gladly be available for a teleconference to further review the details of this finding and provide clarity or additional assurances ensuring data integrity.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M (b) (6)
F 224-554-7870
sandra.cosner@takeda.com
www.tgrd.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Friday, January 04, 2013 6:36 AM
To: Cosner, Sandra (TGRD)
Subject: NDA22271 alogliptin: Information Request

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/07/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Friday, January 04, 2013 7:36:00 AM

Dear Sandy,

Please provide a response to the following Information Request for alogliptin NDA22271. Send your response to this Information Request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Monday, January 7, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. Provide an updated table to the one below since it has now been over 6 months since the database cut-off and as they point out, there was case 8413-006/402 occurring after that date.

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

2. Provide the patient ID and narratives for the patients with ALT > 10xULN and for any other cases of ALT>3xULN with 2xULN that may have occurred in EXAMINE."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/04/2013

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin: Information Request
Date: Wednesday, January 02, 2013 12:40:00 PM
Attachments: image005.png
image006.png

Dear Sandy,

Please provide a response to the following questions for alogliptin NDA22271. Send your response to this Information request directly to me via email and officially submit to the relevant NDAs. As we close in on the PDUFA date for review, we ask that you provide your response as early as possible, preferably by Friday, January 4, 2013. Let me know if you have any questions and please confirm receipt of this email notification.

"1. What doses of alogliptin were prescribed to the patients who experienced the two postmarketing events (TCI2011A04573 (fulminant hepatic failure) and TCI2011A06837 (transaminitis and jaundice)?

2. Please provide summary of incidence of transaminase elevations as in the following table but broken down by actual daily alogliptin doses used in all these trials (6.25, 12.5, 25 and 50 mg).

Table 3.b Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Controlled Phase 2 and 3 Study Group)

	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
Parameter	All Comparators (d) N=5786	All Alogliptin (e) N=9608	All Comparators N=5786	All Alogliptin N=9608	All Comparators N=5699	All Alogliptin N=9495
ALT (>3×ULN) and total bilirubin >2×ULN	0	0	3 (0.05) [0.07]	2 (0.02) [0.03]	2 (0.04)	1 (0.01)
ALT (>20×ULN)	0	0	3 (0.05) [0.07]	3 (0.03) [0.04]	2 (0.04)	2 (0.02)
ALT (>10×ULN)	1 (0.02)	3 (0.03)	5 (0.09) [0.11]	12 (0.12) [0.17]	3 (0.05)	4 (0.04)
ALT (>5×ULN)	2 (0.03)	6 (0.06)	17 (0.29) [0.39]	34 (0.35) [0.49]	7 (0.12)	11 (0.12)
ALT (>3×ULN)	16 (0.28)	41 (0.43)	89 (1.54) [2.04]	126 (1.31) [1.82]	30 (0.53)	32 (0.34)
ALP (>3×ULN)	3 (0.05)	3 (0.03)	9 (0.16) [0.21]	18 (0.19) [0.26]	5 (0.09)	8 (0.08)
Bilirubin, total (>2.0 mg/dL)	11 (0.19)	19 (0.20)	42 (0.73) [0.96]	55 (0.57) [0.79]	22 (0.39)	24 (0.25)

Source: IAS Table 5.1.1, 5.1.2, 5.6.1, and 5.6.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in brackets.
(c) Last assessment is the last assessment of ALT on or before the last dose of study medication.
(d) The All Comparators grouping combines placebo and active comparator dose groups.
(e) The All Alogliptin grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

3. In the following table of transaminase elevations in EXAMINE provided by Takeda, did this table include case 8413-006/402? "

Table 3.f Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002	Placebo N=1980	Alogliptin N=2002
ALT >3×ULN and total bilirubin >2×ULN	0	0	0	0	0	0
ALT >20×ULN	0	0	0	0	0	0
ALT >10×ULN	1 (0.05)	2 (0.10)	0	4 (0.20)	0	1 (0.05)
ALT >5×ULN	2 (0.10)	2 (0.10)	4 (0.20)	13 (0.65)	1 (0.05)	4 (0.20)
ALT >3×ULN	10 (0.51)	14 (0.70)	24 (1.21)	30 (1.50)	7 (0.35)	9 (0.45)

Source: IAS Table 5.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) Endpoint is defined as the last value collected within 7 days of the last dose of study medication.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
01/02/2013

From:	Whitehead, Richard
To:	Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc:	Barnes-Glait, Diane (TGRD) (diane.barnes-glait@takeda.com)
Subject:	NDA22271/22426/203414 alogliptin: draft labeling
Date:	Thursday, December 20, 2012 10:55:00 AM
Attachments:	alo-met- 20Dec12-package-insert.doc alo-pio-20Dec12-draft-package-insert.doc alogliptin 20Dec12-PI.doc

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Sandy,

Please find attached our first round of edits to the package inserts for alogliptin, alogliptin-pioglitazone, and alogliptin-metformin, incorporating comments from Clinical, CMC, Pharm/Tox, Statistics and Clinical Pharmacology. As previously mentioned we were able to spend more time reviewing the alogliptin label, therefore we ask you to carry all relevant comments from the alogliptin label to the alogliptin-pioglitazone and alogliptin-metformin labels.

We have one note from the nonclinical review team:

"We have provided editorial changes to the pregnancy (8.1) and carcinogenesis (13.1) sections of the alogliptin monotherapy (NESINA) and alogliptin + pioglitazone (OSENI) labels. We feel the nonclinical data in question does not need to be described because the animal findings at the high exposure margins would not provide additional meaningful information about clinical risks. "

We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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. Because of the tight timelines was ask the you complete your review and return comments by **noon, Thursday, January 3rd**.

We also request that you convert the alogliptin and alogliptin-metformin Patient Package Inserts into MedGuides and update the alogliptin-pioglitazone MedGuide. Because of the serious risk of hepatotoxicity associated with the use of alogliptin and the serious risk of pancreatitis related to the DPP4 class, FDA has determined that alogliptin and alogliptin/metformin will be required to have a Medication Guide. Additionally, because of the serious risks of hepatotoxicity and heart failure associated with the use of alogliptin/pioglitazone and the serious risk of pancreatitis related

to the DPP4 class, FDA has determined that alogliptin/pioglitazone will be required to have a Medication Guide (which it does, but needs to include the additional risks).

Please confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
12/20/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 Nesina: Information Request
Date: Monday, December 03, 2012 10:04:00 AM

Sandy,

As mentioned on Friday, Dr. Parks will no longer be available because of another commitment. However the purpose of the call was to discuss one case and possibility of hepatitis E Virus (HEV) infection that is outlined in this email.

Please refer to your NDA22271 amendment submitted on November 9, 2012. FDA wants to better understand the of cause of liver injury in patient 8413-006/402. If Takeda has stored blood from patient 8413-006/402 prior and after to receipt of the study drug, we encourage you to test for HEV markers, HEV RNA, and IgM anti-HEV that later reverts to IgG anti-HEV. We ask that you provide your laboratory results in a timely manner.

If no blood from patient 8413-006 has been stored, a current blood sample from that patient should be obtained . We therefore encourage you to ask patient 8413-006/402 to return for an additional blood test. Again, this sample should be tested from markers of HEV, anti-HEV IgM and IgG.

Dr. Parks had originally planned to be on this call only to raise your awareness to how important it is for you to obtain a definitive answer on whether patient 8413-006/402 had acute hepatitis E.

The review of alogliptin will soon be nearing completion and to complete the review we feel it is very important to request the additional analysis. If you have any follow-up questions send them via email. If we are not able to answer them through email we will set up a telephone call at a letter point.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
12/04/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22271 **GENERAL ADVICE**

Takeda Pharmaceuticals, U.S.A., Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) 25 mg, 12.5 mg, and 6.25 mg tablets.

We also refer to your January 24, 2012 submission containing revised container labels and carton labeling.

We have reviewed the referenced material and have the following comment and recommendation:

(b) (4)

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

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
11/15/2012

From: Cosner, Sandra (TGRD)
To: Whitehead, Richard
Subject: RE: NDA22271/NDA22426/NDA203414 Request for Information
Date: Tuesday, October 30, 2012 3:11:24 PM

Thank you Rich. I am confirming receipt of this email. The team will work on this response and get back with you as soon as we are able to.
Thanks
Sandy

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Monday, October 29, 2012 2:41 PM
To: Cosner, Sandra (TGRD)
Cc: Villinski, Allison (TGRD)
Subject: NDA22271/NDA22426/NDA203414 Request for Information

NDA22271 alogliptin
NDA22426 alogliptin/pioglitazone
NDA203414 alogliptin/metformin

Dear Ms. Cosner:

In reference to NDA 22271, NDA22426, and NDA203414, please see the request for information below. We ask that you provide responses at your earliest opportunity. Let me know if you have any questions and please confirm receipt of this email.

"In your October 5, 2012 Information Request Response, you stated that subject 8413-006/402 was on atorvastatin which was discontinued on day 207. Provide further details regarding the atorvastatin administration, including the date the patient was initially administered atorvastatin, whether atorvastatin was administered consistently from the start date to day 207 (or whether there were any gaps), and any other information you have regarding this case that you have not yet submitted to us.

Submit each individual LSEC committee members' assessment of subject 8413-006/402 .

On October 10, 2012, you submitted follow up safety report TCI2012A05429. Submit any additional information you have regarding this case."

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
11/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22271 **GENERAL ADVICE**

Takeda Pharmaceuticals, U.S.A., Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) 25 mg, 12.5 mg, 6.25 mg tablets.

We also refer to your January 24, 2012 submission, containing revised container labels and carton labeling.

We have reviewed the referenced material and have the following comments and recommendations:

1) All Container Labels and Carton Labeling: All Strengths
   Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXX-xx). Pharmacists use the middle portion of the NDC number to ensure the correct product is dispensed.

2) Blister Card Container Labels: 12.5 mg and 25 mg Strengths
   The blister cards use [redacted] (b) (4) on the packaging. This presentation decreases the contrast and visibility of important information, which affects readability. Remove [redacted] (b) (4) of the packaging and follow the bottle presentation with partial coloration (i.e. color block around the strength presentation) and white background with black lettering.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

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
10/28/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22271

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Takeda Global Research & Development Center, Inc
One Takeda Parkway
Deerfield, IL 60015

Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated July 25, 2011, received July 25, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Alogliptin Tablets, 6.25 mg, 12.5 mg, and 25 mg. Please also refer to your complete Class 2 resubmission to this NDA, dated and received July 26, 2012.

We also refer to:

- Your initial proprietary name submission, dated July 25, 2011, for the proposed name Nesina;
- Our initial correspondence dated October 17, 2011, finding this proposed proprietary name conditionally acceptable;
- Your submission dated and received August 1, 2012, requesting re-review of your proposed proprietary name, Nesina.

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

The proposed proprietary name, Nesina, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your August 1, 2012, 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 Richard Whitehead at (301) 796-4945.

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

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/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
10/26/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc: Hai, Mehreen
Subject: FW: Questions for NDA 22271 regarding potential amendment
Date: Tuesday, October 16, 2012 6:41:00 AM

Hi Sandy,

We received feedback on your questions (see below in red). Let me know if you have additional questions.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, October 11, 2012 3:14 PM
To: Hai, Mehreen; Whitehead, Richard
Cc: Villinski, Allison (TGRD)
Subject: Questions for NDA 22271 regarding potential amendment

Dear Mehreen and Rich,
Thank you for talking with Allison and I this afternoon regarding the status of the alogliptin NDA 22-271. As requested, I am providing a follow-up email of our discussions and questions so that you can reach out to the appropriate individuals for their guidance.

As we mentioned, Takeda has learned that FDA is scheduling an inspection of the [redacted] (b) (4)) site in December 2012 based on our August 27th submission of the (b) (4) contact information. Takeda has also learned that a final decision on the status of the Osaka site based on a recent FDA inspection will likely be made in the next two to three months. Given the current PDUFA timing for the aloglipin family and the timing associated with the decision regarding the Osaka facility, we wanted to discuss possible pathways moving forward.

[redacted] (b) (4) will be submitted after October 29 (within 90 days of PDUFA). Pleast note that even if the CMC documentation for (b) (4) is not provided at the end of October, Takeda [redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

We again greatly appreciate you taking the time to have this discussion with us and also reaching out to other groups to provide us guidance on how the Agency will likely handle these different scenarios.

Best regards,

Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M (b) (6)
F 224-554-3646
sandra.cosner@takeda.com
www.tgrd.com

APPEARS THIS WAY ON ORIGINAL

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/s/

RICHARD E WHITEHEAD
10/16/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 alogliptin Information Request
Date: Wednesday, September 26, 2012 11:31:00 AM

NDA22271 alogliptin Information Request

Dear Sandy:

FDA is requesting the following information in reference to the NDA22271 Fourth Japanese Periodic Safety Update Report for alogliptin:

"In Table 19 of the Fourth Japanese Periodic Safety Update Report for alogliptin, you list 15 nonserious hepatic adverse events. Please answer the following for these cases:

- Did any of the nonserious cases have biochemical Hy's law?
- Did the event resolve? If yes, was use of alogliptin continued?
- If alogliptin was discontinued, was the patient rechallenged?"

Submit your response as amendments to the 3 alogliptin NDAs. Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/DMEP; 10903 New Hampshire Avenue, WO22 Room 3121, Silver Spring, MD 20993; 301.796.4945; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/26/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 PSUR: Information Request
Date: Monday, September 24, 2012 7:40:00 AM

NDA22271: Periodic Safety Update Report for alogliptin (4th Report)

Sandy,

FDA is requesting that you provide the information below that pertains to the NDA22271 periodic safety update report covering the period of 16 October 2011 to 15 April 2012:

"Please submit thorough case narratives for all subjects listed in the Summary of Clinical Safety Tables 3.c and 3.d. Include both subject number and study case number, if applicable."

Let me know if you have any questions. Please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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RICHARD E WHITEHEAD
09/24/2012

From: Whitehead, Richard
To: Cosner Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271 and NDA 203414 Study SYR-322_309 Reviewer Comments
Date: Friday, September 21, 2012 9:33:00 AM

NDA 22271 alogliptin
NDA 203414 alogliptin/metformin

Sandy,

We have the following preliminary statistical review comments, based on the NDA22271 and NDA203414 synopsis of Study SYR-322_309:

(b) (4)

(b) (4)

Let me know if you have any questions. Please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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RICHARD E WHITEHEAD
09/21/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA22271/NDA22426 Information Request
Date: Friday, September 21, 2012 7:49:00 AM

NDA 22271 alogliptin

NDA 22426 alogliptin/pioglitazone FDC

Sandy,

FDA is requesting that you provide the information below to NDA 22271 and NDA 22426.

"On August 16, 2012, you submitted an updated pediatric deferral request containing revised clinical study dates to alogliptin/metformin FDC NDA 203-414 but not alogliptin NDA 222-71 or alogliptin/pioglitazone FDC NDA 22-426. Please submit the updated pediatric deferral information to NDAs 22-271 and 22-426."

Let me know if you have any questions. Please confirm receipt of this email.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;

(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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RICHARD E WHITEHEAD
09/21/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Subject: NDA 022426 and NDA 022271 Acknowledge- Class 2 Response Letters
Date: Wednesday, September 12, 2012 2:50:00 PM

NDA 022426
NDA 022271

Dear Ms. Cosner:

In reference to the Acknowledge- Class 2 Response Letters sent for NDA 022426 and NDA 022271 on August 10, 2012, please note that the user fee goal date is not correct in each letter. The correct user fee goal date for NDA 022426 should state **January 27, 2013** and for NDA 022271 the date should be **January 26, 2013**. Let me know if you have any questions. Please confirm receipt of this email

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
09/13/2012

From: Whitehead, Richard
To: "Cosner, Sandra (TGRD)"
Cc: Hai, Mehreen
Subject: RE: alogliptin NDA 22-271- Clarification regarding major amendment (b) (4)
Date: Wednesday, August 22, 2012 8:34:00 AM

Sandy,

Here is a response to your questions:

(b) (4)

Let me know if you have any additional questions. Please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Tuesday, August 21, 2012 4:12 PM
To: Whitehead, Richard
Cc: Cosner, Sandra (TGRD); Hai, Mehreen
Subject: alogliptin NDA 22-271- Clarification regarding major amendment (b) (4)

Hi Rich,

As a follow up to our phone call this afternoon, I am providing you the questions we discussed via email.

(b) (4)

(b) (4)

(b) (4)

Upon consideration of another scenario, if Takeda were to submit a major amendment following October 26 (within 90 days of the PDUFA) (b) (4) at a later date following the major amendment impact the review or timeline of the NDA?

Thanks in advance for your insights and assistance. Takeda is hoping that being transparent and proactive with regards to the review of the alogliptin NDA the Agency and Takeda can partner to

determine the most appropriate regulatory pathway.

Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
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T 224-554-1957
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sandra.cosner@takeda.com
www.tgrd.com

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/s/

RICHARD E WHITEHEAD
08/24/2012

From: Whitehead, Richard
To: Cosner, Sandra (TGRD) (sandra.cosner@takeda.com)
Cc: Hai, Mehreen
Subject: FW: Follow up to yesterday"s teleconference NDA 22-271
Date: Thursday, August 16, 2012 12:16:00 PM

Hi Sandy,

Please see responses to your questions below in red.

Regards,
Rich

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Tuesday, August 14, 2012 11:47 AM
To: Whitehead, Richard
Cc: Hai, Mehreen; Cosner, Sandra (TGRD)
Subject: Follow up to yesterday's teleconference NDA 22-271

Hello Rich,
Thank you and the team again for quickly setting up the teleconference yesterday and for the very informative discussion.

As discussed at the teleconference yesterday and with you briefly this morning, Takeda would like clarification on the process if an unsolicited major amendment was submitted in the near future. If the Agency determines to review the amendment, the MAPP 6010.8 appears to indicate the original timeline would no longer apply regardless of the timing the amendment occurred (within or outside of the 90 days), However, Mehreen indicated the Agency would maintain the original PDUFA date (which in this case is January 26th). Please confirm if the January 26th PDUFA date would still be applicable if an unsolicited major amendment was submitted more than 90 days prior to PDUFA or if the Agency is no longer held to that date since it is an unsolicited amendment.

Yes, the PDUFA date of January 26th would still apply. A major amendment can only alter the PDUFA goal if it occurs within 90 days of the date, irrespective of whether it is solicited or unsolicited. What the MAPP refers to as "timeline" are the interim milestone dates on which FDA is expected to communicate with the applicant, such as the expected date that FDA sends proposed labeling to the applicant, and these may or may not change based on how the division's review deadlines have changed due to the major amendment. The "timeline" does not mean the PDUFA date, which has to be either the original PDUFA date (January 26th), or the 3-month extended PDUFA date (April 26th), depending on whether or not the division accepts the amendment for review.

In addition, if a major amendment was submitted after October 26 (within 90 days of PDUFA), and the Agency accepts it for review, would Takeda be formally notified of the review extension? If so, when would the sponsor receive the notification?

Yes, Takeda would be formally notified usually within one week. After receiving the amendment,

we will review the information to make sure it is adequate for review and if it is, a formal letter will be sent.

Could Takeda expect that this extension would be 3 months?

The extension would be 3 months

If it the major amendment was not accepted and therefore the January 26th PDUFA was not extended, would Takeda be notified prior to an action letter?

If the major amendment was submitted in the last 90 days and we decide to not include it in our review and therefore not extend the date, we will inform Takeda soon thereafter. However, if the major amendment is submitted next week, as you originally suggested, and there is no option of extending the PDUFA date, we may reserve the decision on whether or not to include the amendment in our review until closer to the action date (based on whether or not it seems likely that we will miss our action date if we do include the amendment in our review).

Based on the discussion yesterday, it seems as though if the major amendment occurred immediately after October 26th (and it was accepted with a 90 day extension) this would allow 6 months for the review and [redacted] (b) (4), which is the same timing as the Agency outlined in which the NDA Re-submission was withdrawn and then sent in again.

This would be fine. [redacted] (b) (4)

I greatly appreciate any feedback you can provide on these questions.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
T 224-554-1957
M [redacted] (b) (6)
F 224-554-3646
sandra.cosner@takeda.com
www.tgrd.com

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/s/

RICHARD E WHITEHEAD
08/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271

ACKNOWLEDGE – CLASS 2 RESPONSE

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

We acknowledge receipt on July 26, 2012, of your July 26, 2012, resubmission of your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets.

We consider this a complete, class 2 response to our action letter dated April 25, 2012. Therefore, the user fee goal date is **January 26, 2012**.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEHREEN HAI
08/10/2012

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)"
Subject: RE: Request for Teleconference for alogliptin NDA 22-271
Date: Wednesday, August 08, 2012 10:52:00 AM

Hi Sandy,
Please see our response to your inquiry below:

Your proposed major amendment to the NDA, [redacted] (b) (4), does not address any deficiency discussed in our April 25, 2012, Complete Response letter. This proposal was not discussed with us prior to our receipt of your resubmissions and would therefore be considered an unsolicited amendment, therefore we cannot guarantee its evaluation during this review cycle. Furthermore [redacted] (b) (4)

Please let me know if you need to talk about this further.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Tuesday, August 07, 2012 1:58 PM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: Request for Teleconference for alogliptin NDA 22-271

Dear Mehreen,

Takeda has been considering the potential for adding [redacted] (b) (4) we would like to request a teleconference with you and the appropriate FDA CMC reviewers to discuss the rationale and plans for this submission and any implications this may have on the current new drug application.

Please let me know if the Agency will grant this teleconference to discuss this potential plan with the appropriate individuals at FDA and Takeda in the near future.

Thank you.

Kind regards,

Sandy

Sandra D. Cosner, RPh
Associate Director
Regulatory Affairs

Takeda Global Research & Development Center, Inc.
One Takeda Parkway
Deerfield, IL 60015
U.S.A.
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/s/

MEHREEN HAI
08/08/2012

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Monday, July 30, 2012 1:36 PM
To: 'sandra.cosner@takeda.com'
Cc: Hai, Mehreen
Subject: Information needed for NDAs 22-271 and 22-426

Dear Sandra,

We are reviewing the CMC section of your NDAs mentioned above and need the following clarification and information from you as soon as possible:

1. Include all the facilities information (facility address, contact name, phone number and fax number) in the Form 356H and clearly state whether there is any change in the commercial manufacturing or testing facility since the last submission for both the NDAs (i.e. new sites or deleted sites).
2. Please state if the resubmission includes any new CMC information.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested. Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
07/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 29, 2012. The purpose of the meeting was to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies.

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

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes for End-of-Review meeting held on June 29, 2012

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Review
Meeting Date and Time:	June 29, 2012, 2:00 p.m. – 3:00 p.m.
Meeting Location:	White Oak Campus, Silver Spring, MD
Application Numbers:	NDA 022271; NDA 022426
Product Names:	Alogliptin tablets; Alogliptin-pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
Jean-Marc Guettier, M.D.	Diabetes Clinical Team Leader, DMEP
Karim Calis, Pharm.D.	Acting Diabetes Clinical Team Leader, DMEP
Lisa Yanoff, M.D.	Clinical Reviewer, DMEP
Janice Derr, Ph.D.	Biostatistics Reviewer, Division of Biometrics II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Eugenio Andraca-Carrera, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology 2
Manoj Khurana, Ph.D.	Reviewer, Division of Clinical Pharmacology 2
Leonard Seeff, M.D.	Hepatologist, Office of Surveillance and Epidemiology (OSE)
Christian Hampp, Ph.D.	Pharmacoepidemiologist, Division of Epidemiology 1 (OSE)
Caitlin Knox	Fellow, Division of Epidemiology 1 (OSE)

SPONSOR ATTENDEES (Takeda Representatives and Consultants)

Sandra Cosner, R.Ph.	Associate Director, Regulatory Affairs
Penny Fleck, M.T.	Senior Director, Clinical Science
Thomas Harris, R.Ph.	Global Regulatory Head, Regulatory Affairs
Qais Mekki, MD, Ph.D.	Vice President, Pharmacovigilance
Melvin Munsaka, Ph.D.	Senior Manager, Safety Statistics
Azmi Nabulsi, M.D.	President, Takeda Global Research and Development
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Neila Smith, M.D.	Executive Medical Director, Pharmacovigilance
Nancy Siepman, Ph.D.	Vice President, Analytical Sciences
Thomas Strack, M.D.	Therapeutic Area Head, Diabetes, Pharmaceutical Drug Development
Allison Villinski, M.S.	Director, Regulatory Affairs
(b) (4)	(Consultant)
(b) (4)	(Consultant)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (proprietary name: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009, for NDA 022426.

TGRD resubmitted both NDAs on July 25, 2011. A complete response letter issued for both NDAs on April 25, 2012.

The purpose of this meeting is to discuss the resubmissions that will respond to the April 25, 2012, complete response letter.

2. DISCUSSION

The sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the sponsor on June 26, 2012, follow in **bold** font. A summary of the meeting discussion is indicated in *italicized* font.

Preliminary Discussion: Takeda summarized the timeline of the alogliptin NDA. A total of 9,857 subjects have been exposed to alogliptin in the April 2012 IAS safety update (6,934 subject-years). (b) (4) *stated that, if alogliptin is associated with hepatotoxicity, it is a rare event (1:1000,000).* (b) (4) *acknowledged there was an imbalance in serum ALT>10x ULN in the clinical trial database and stated that the risk of hepatotoxicity cannot be excluded. However, he believes the risk is finite and not severe.*

Question 1: Provided that the Agency's review of the new clinical and postmarketing data are consistent with Takeda's interpretation of the data summarized in this briefing document, does the Agency agree that the information planned for submission can provide the additional reassurance the FDA is seeking on the hepatic safety profile of alogliptin in order to complete the review and approve the applications?

FDA Preliminary Response: Whether or not the information planned for submission can provide the additional reassurance necessary for approval is a review issue. However, the April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.

Meeting Discussion: *The Agency and Takeda agreed that information similar to that contained in the meeting document could be submitted to the NDAs as a complete response. Although final determination of whether such submission is a Type 1 or 2 complete response would be made after submission, it would likely be a Type 2 response with a six-month review clock because it contains clinical data.*

Question 2: Takeda's understanding per the CRL [complete response letter] is that the resubmission must be supported by the absence of any postmarketing reports of severe drug-induced liver injury events that are convincingly linked to alogliptin therapy (e.g., leading to death or liver transplantation). Takeda would like to clarify that any such case would need to be devoid of confounding factors prior to the Agency attributing the event to alogliptin (or any drug) therapy. This should especially be the case in light of the current lack of liver case imbalance in the clinical database. Does the Agency agree?

FDA Preliminary Response: A case need not be devoid of all confounding factors prior to attributing the event to alogliptin therapy. Although the assessment of potential drug-induced liver injury is grounded in the scientific grading system developed by the National Institutes of Health Drug-Induced Liver Injury Network (DILIN) Study Group, the Agency recognizes that, at times, the final classification of a particular case may be a matter of opinion. Consistent with the DILIN Study Group grading system, an attempt will be made to assess the effect of potential confounders before attributing causality to drug therapy.

Meeting Discussion: *There was no discussion of Question 2.*

Question 3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

FDA Preliminary Response: We generally agree with the proposed structure and contents of the NDA resubmission. However, the Summary of Clinical Safety in Module 2 should also contain the following:

- **Summary of deaths**
- **Updated summary tables for cardiovascular safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia. Please include a summary of the changes from the previous submission.**

Pre-Meeting Response from Takeda: *In response to Question #3, Takeda would like to clarify how each of the requested topics will be addressed within 2.7.4. As had been done previously, narratives for all deaths, serious adverse events and adverse events leading to discontinuation will be included. For the Controlled Phase 2/3 dataset proposed for the NDA re-submissions, any key differences from the July 2011 NDA re-submissions will be highlighted in text.*

Does the Agency agree with the following proposals for each of the topics below?

• Summary of deaths: A summary by System Organ Class (SOC) and Preferred Term (PT) for Controlled Phase 2/3 Group will be provided.

• CV Safety: An updated MACE Analysis using adjudicated CV events would include data from Study 402 (July 2011 based on pre-specified interim analysis), 305 (1 year pre-planned interim data cut), 302 (completed clinical study) and those studies previously included in the July 2011 NDA re-submissions. Please note that the CV SOC will be presented and discussed in AE and SAE sections of 2.7.4.

• Renal Safety: The renal data based on clinical laboratory values will be updated for the Controlled Phase 2/3 data set.

• Hypersensitivity: The hypersensitivity section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.

• Skin Lesions: The hypersensitivity cluster includes angioedema, anaphylactic reaction and severe cutaneous skin reactions (which covers rash and puritis). Does the Agency agree this cluster is sufficient with regards to skin lesions?

• Pancreatitis: The pancreatitis section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.

• Infections: Adverse events will be presented by SOC of Infections and Infestations similar to that in July 2011 NDA re-submissions.

• Malignancy: Takeda will utilize the SMQ of malignancies similar to that included in the July 2011 NDA re-submissions.

• Fractures: Can the Agency clarify if this request is due to pioglitazone component of the fixed dose product? If so, there are no new studies with the alogliptin/pioglitazone combination since

the July 2011 resubmission; therefore no new information would be included in the upcoming NDA re-submissions.

• Hypoglycemia: The studies with similar definitions of hypoglycemia will be integrated; however some studies over the course of the program have a different definition of hypoglycemia and Takeda proposes to discussed those results individually.

Meeting Discussion: *The Agency agreed with Takeda's Pre-Meeting Response, although it was agreed that Takeda would also submit an analysis of Potential Cutaneous Drug Reactions (PCDR's) as it had done in the previous NDA submission. The Agency clarified that the fracture request was due to the pioglitazone component of the fixed-dose product, therefore the Agency understands that no new updates will be provided for fractures as there are no additional clinical data with alogliptin-pioglitazone.*

The Agency stated that it recently received guidance from FDA Counsel and staff in the Division of Information and Disclosure Policy on whether interim data from the ongoing cardiovascular (CV) trial can be withheld from public disclosure. It is not CDER's practice to redact summary data from approval documents when the Center relies on such information to make an approval decision. CDER is committed to transparency of our decision-making processes. We believe that it is important for the public to understand that CDER carefully evaluated the benefits and risks of a particular therapy for a certain condition of use and to understand how we came to our decision that the benefits outweigh the risks. Furthermore, FDA's regulations favor disclosure of information in an application after the application has been approved and identify the summary safety data that are subject to disclosure immediately upon issuance of an approval letter. The Agency is not inclined to place the data in the label.

Takeda inquired whether other regulatory agencies share a similar view regarding disclosure policy as FDA. The Agency is aware that other regulatory agencies are also inclined toward complete disclosure and that, in some cases, these regulatory agencies would also consider labeling of interim data.

Question 4: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, we agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable.

Meeting Discussion: *There was no discussion of Question 4.*

Question 5: Does the Agency agree with Takeda's plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Yes, we agree with the plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not to submit a separate summary report of the integrated analyses within Module 5.3.5.3.

Meeting Discussion: *There was no discussion of Question 5.*

Question 6: Since Studies 402 and 305 are still ongoing, Case Report Forms for these studies will not be included in the NDA resubmissions as agreed upon for the July 2011 resubmission with regard to Study 402. Is this proposal acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable. However, additional information may be requested if it is needed.

Meeting Discussion: *There was no discussion of Question 6.*

Question 7: Takeda does not plan to summarize data from the recently completed, 4-year, open-label extension study (012) within 2.7.4. However, the final clinical study report will be provided in the resubmission. Is this approach acceptable to the Agency?

FDA Preliminary Response: Yes, we agree with your plan to not summarize data from uncontrolled, open-label extension study (012) within 2.7.4.

Meeting Discussion: *There was no discussion of Question 7.*

Question 8: Takeda plans to update the efficacy section of the alogliptin package insert based on data from Studies MET-302 (b) (4) Since the efficacy information is not integrated, Takeda does not plan to include a Clinical Summary of Efficacy (2.7.3) in the NDA resubmission but will rely on the data included in the individual clinical study reports. Is the Agency agreeable to this approach?

FDA Preliminary Response: (b) (4) **, we agree with your plan to update the efficacy section of the alogliptin package insert with data from completed study MET-302. Since the efficacy information is not integrated, we agree with your plan to not include a Clinical Summary of Efficacy (2.7.3) in the resubmission.**

Meeting Discussion: (b) (4)

The Agency and Takeda agreed that safety (b) (4) *data from ongoing study 305 could be included in the label.*

Question 9: Due to the fact that labeling negotiations had initiated under the previous review cycle and there are still some aspects other than safety that need to be discussed, Takeda proposes not to include Structured Product Labeling (SPL) in the NDA resubmissions. Takeda will provide the package insert information in SPL format once labeling language has been agreed upon by both Takeda and the Agency. Is this acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable.

Meeting Discussion: *There was no discussion of Question 9.*

Question 10: Does the Agency agree with the process for enhanced monitoring of postmarketing liver-related cases?

FDA Preliminary Response: Yes, we agree with the process for enhanced monitoring of postmarketing liver-related cases.

Meeting Discussion: *There was no discussion of Question 10.*

Question 11: During the course of the review of the NDA resubmissions, spontaneous reports related to hepatic safety may be received. Takeda will continue to expedite these reports to the INDs and NDAs, as previously agreed. However, in an effort to provide a meaningful adjudication of these cases, Takeda often needs adequate time to gather relevant information for an individual postmarketing case. Therefore, the LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. Is this approach reasonable to the Agency?

FDA Preliminary Response: Yes, your approach is reasonable. However, additional information may be requested as needed.

Meeting Discussion: *There was no discussion of Question 11.*

Question 12: If during the course of the review of the NDA resubmissions, there is striking disagreement between the Agency and the LSEC on a particular liver safety case(s), would the Agency consider discussing the case(s) with the LSEC (and Takeda)?

FDA Preliminary Response: Yes, we may consider discussing case(s) with you and the LSEC. However, the purpose of such discussion would be to share information to ensure that both you and the Agency have all currently available data to aid decision-making. The objective of the meeting would not be to obtain a consensus of opinion on liver case(s) or to discuss upcoming regulatory decision(s).

Meeting Discussion: *There was no discussion of Question 12.*

Question 13: Is the Agency agreeable to discussing how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End of Review meeting?

FDA Preliminary Response: Yes, we may discuss how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End-of-Review meeting.

Meeting Discussion: *It was agreed that Takeda could submit data from the April 2012 IAS Update to the alogliptin/metformin FDC NDA as a major amendment. The goal dates for the alogliptin/metformin FDC NDA and the alogliptin and alogliptin/pioglitazone FDC NDAs will not be perfectly aligned and discretion may be taken with regard to the completion dates for any one of these NDAs. However, it was stated that approval of the FDC NDAs is contingent on the Agency's conclusion that the deficiencies for the alogliptin NDA have been adequately addressed and any timing of approval would be based on such a conclusion.*

Question 14: In the 25 April 2012 Complete Response Letter, there are questions related to the alogliptin pediatric program. Takeda is currently planning on initiating the phase 3 program in early 2013 due to Pediatric Committee requirements. In order to incorporate the Agency's feedback into the studies before they are started, Takeda plans to submit responses to the pediatric questions in an IND Amendment. Is this proposal acceptable?

FDA Preliminary Response: You may submit responses to the pediatric questions in an IND amendment. However, please note that a pediatric postmarketing study requirement cannot be issued until an NDA is approved. Please also submit relevant information to the NDA.

Meeting Discussion: *Takeda stated that it wishes to conduct a global pediatric program. As a result, it may need to initiate pediatric study(ies). It asked for the Agency's cooperation in developing the global pediatric development program. The Agency agreed.*

Additional Preliminary Comment from FDA: Please explain whether or not you plan to (b) (4) (b) (4) **could possibly offset the potential liver liability.**

Meeting Discussion: *There was lengthy discussion regarding the CV protocol.* (b) (4) *is planned, if the 1.3 goal is met. However, it was not clear if this was a modification to the previous CV protocol and statistical analysis plan.* (b) (4) *akeda will consider protocol revisions to the pre-planned interim analyses and will submit any proposed changes for review by the Agency. The Agency*

agreed to review the protocol and expressed that any revision to the interim analyses include clearly defined timing of the interim look, stopping rules, and alpha-spending function.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

Slides presented by the sponsor at the meeting are attached.

NDAs 22-271 and 22-426

FDA End-of-Review Meeting for alogliptin and alogliptin/pioglitazone

June 29, 2012

Takeda Global Research & Development Center, Inc.

Alogliptin End of Review Meeting - June 29, 2012

- Question 1– adequacy of clinical and postmarketing data to address complete response
- Question 3 – proposed content of the resubmission
- Question 8 – inclusion of efficacy data for studies 302 [redacted] (b) (4) in the package insert
- Question 13 – path forward for the alogliptin/metformin NDA review cycle
- Question 14 – pediatric program
- Additional Comment: regarding [redacted] (b) (4) for EXAMINE trial

Overall Alogliptin Exposure in Controlled Phase 2/3 Studies

	Alogliptin Total Subject Numbers (n)	Alogliptin Cumulative Exposure (Subject-Years)
July 2011 (NDA Re-submission)	5232	2498
November 2011 (Response to 24 October 2011 Information Request)	7229	3378
April 2012 IAS (Proposed NDA Re-submission)	9857	6934

The proposed 2012 re-submission represents a 40% increase in incidence and 100% increase in exposure since November 2011.

Number of Subjects Meeting Markedly Abnormal ALT Criteria in Phase 2/3 Controlled Studies

	November 2011		April 2012 IAS	
	Number (%) of Subjects w/ >=1 Markedly Abnormal Result (95% Exact CI)			
Parameter	**All Comparators (N=4074)**	**All Alogliptin (N=7011)**	**All Comparators (N=5786)**	**All Alogliptin (N=9608)**
ALT>20xULN	0 (0, 0.09)	2 (<0.1) (0, 0.10)	3 (0.1) (0.01, 0.15)	3 (<0.1) (0.01, 0.09)
ALT>10xULN	0 (0, 0.09)	8 (0.1) (0.05, 0.22)	5 (0.1) (0.03, 0.20)	12 (0.1) (0.06, 0.22)
ALT>5xULN	6 (0.1) (0.05, 0.32)	21 (0.3) (0.19, 0.46)	17 (0.3) (0.17, 0.47)	34 (0.4) (0.25, 0.49)
ALT>3xULN	39 (1.0) (0.68, 1.31)	71 (1.0) (0.79, 1.28)	89 (1.5) (1.24, 1.89)	126 (1.3) (1.09, 1.56)

Note: CIs calculated using Binomial Distribution.

Question #3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

- Narratives for all deaths, serious adverse events and adverse events leading to discontinuation will be included.

- For the Controlled Phase 2/3 dataset proposed for the NDA re-submissions, any key differences from the July 2011 NDA re-submissions will be highlighted in text.

- **Summary of deaths:** A summary by System Organ Class (SOC) and Preferred Term (PT) for Controlled Phase 2/3 Group will be provided.

- **CV Safety:** An updated MACE Analysis using adjudicated CV events would include data from Study 402 (July 2011 based on pre-specified interim analysis), 305 (1 year pre-planned interim data cut), 302 (completed clinical study) and those studies previously included in the July 2011 NDA re-submissions. The CV SOC will be presented and discussed in AE and SAE sections of 2.7.4.

- **Renal Safety:** The renal data based on clinical laboratory values will be updated for the Controlled Phase 2/3 data set.

Question #3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

- **Hypersensitivity:** The hypersensitivity section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.
- **Skin Lesions:** The hypersensitivity cluster includes angioedema, anaphylactic reaction and severe cutaneous skin reactions (which covers rash and pruritus). Does the Agency agree this cluster is sufficient with regards to skin lesions?
- **Pancreatitis:** The pancreatitis section will be updated (both clinical and post-marketing) based on the requests made in the 27 October 2011 Request.
- **Infections:** Adverse events will be presented by SOC of Infections and Infestations similar to that in July 2011 NDA re-submissions.
- **Malignancy:** Takeda will utilize the SMQ of malignancies similar to that included in the July 2011 NDA re-submissions.
- **Fractures:** Can the Agency clarify if this request is due to pioglitazone component of the fixed dose product? If so, there are no new studies with the alogliptin/pioglitazone combination since the July 2011 resubmission; therefore no new information would be included in the upcoming NDA re-submissions.
- **Hypoglycemia:** The studies with similar definitions of hypoglycemia will be integrated; however some studies over the course of the program have a different definition of hypoglycemia and Takeda proposes to discussed those results individually.

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

/s/

MEHREEN HAI
07/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING PRELIMINARY COMMENTS

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to your correspondence dated and received April 27, 2012, requesting an End-of-Review meeting to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies.

Our preliminary responses to your meeting questions are enclosed.

Please provide me with 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, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & 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:	End-of-Review
Meeting Date and Time:	June 29, 2012, 2:00 p.m. – 3:00 p.m.
Meeting Location:	White Oak Campus, Silver Spring, MD
Application Numbers:	NDA 022271; NDA 022426
Product Names:	Alogliptin tablets; Alogliptin-pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.

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 June 29, 2012 at 2:00 p.m. between Takeda Global Research & Development Center, Inc. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of 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). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. 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. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

1. BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

TGRD resubmitted both NDAs on July 25, 2011. A complete response letter issued for both NDAs on April 25, 2011.

The purpose of this meeting is to discuss the resubmissions in response to the complete response letter that issued for NDA 022271 and NDA 022426.

2. QUESTIONS AND PRELIMINARY RESPONSES

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

Question 1: Provided that the Agency's review of the new clinical and postmarketing data are consistent with Takeda's interpretation of the data summarized in this briefing document, does the Agency agree that the information planned for submission can provide the additional reassurance the FDA is seeking on the hepatic safety profile of alogliptin in order to complete the review and approve the applications?

FDA Preliminary Response: Whether or not the information planned for submission can provide the additional reassurance necessary for approval is a review issue. However, the April 2012 IAS exposure sufficiently exceeds that of the July 2011 submission, so as to justify submission of the data for a complete review.

Question 2: Takeda's understanding per the CRL [complete response letter] is that the resubmission must be supported by the absence of any postmarketing reports of severe drug-induced liver injury events that are convincingly linked to alogliptin therapy (e.g., leading to death or liver transplantation). Takeda would like to clarify that any such case would need to be devoid of confounding factors prior to the Agency attributing the event to alogliptin (or any drug) therapy. This should especially be the case in light of the current lack of liver case imbalance in the clinical database. Does the Agency agree?

FDA Preliminary Response: A case need not be devoid of all confounding factors prior to attributing the event to alogliptin therapy. Although the assessment of potential drug-induced liver injury is grounded in the scientific grading system developed by the National Institutes of Health Drug-Induced Liver Injury Network (DILIN) Study Group, the Agency recognizes that, at times, the final classification of a particular case may be a matter of opinion. Consistent with the DILIN Study Group grading system, an attempt

will be made to assess the effect of potential confounders before attributing causality to drug therapy.

Question 3: Does the Agency agree with the proposed structure and contents of the NDA resubmission?

FDA Preliminary Response: We generally agree with the proposed structure and contents of the NDA resubmission. However, the Summary of Clinical Safety in Module 2 should also contain the following:

- **Summary of deaths**
- **Updated summary tables for cardiovascular safety, renal safety, hypersensitivity, skin lesions, pancreatitis, infections, malignancy, fractures, and hypoglycemia. Please include a summary of the changes from the previous submission.**

Question 4: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, we agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable.

Question 5: Does the Agency agree with Takeda's plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Yes, we agree with the plan to summarize safety data within Module 2.7.4 of both NDA resubmissions and therefore not to submit a separate summary report of the integrated analyses within Module 5.3.5.3.

Question 6: Since Studies 402 and 305 are still ongoing, Case Report Forms for these studies will not be included in the NDA resubmissions as agreed upon for the July 2011 resubmission with regard to Study 402. Is this proposal acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable. However, additional information may be requested if it is needed.

Question 7: Takeda does not plan to summarize data from the recently completed, 4-year, open-label extension study (012) within 2.7.4. However, the final clinical study report will be provided in the resubmission. Is this approach acceptable to the Agency?

FDA Preliminary Response: Yes, we agree with your plan to not summarize data from uncontrolled, open-label extension study (012) within 2.7.4.

Question 8: Takeda plans to update the efficacy section of the alogliptin package insert based on data from Studies MET-302 (b) (4). Since the efficacy information is not integrated, Takeda does not plan to include a Clinical Summary of Efficacy (2.7.3) in the NDA resubmission but will rely on the data included in the individual clinical study reports. Is the Agency agreeable to this approach?

FDA Preliminary Response: (b) (4) **we agree with your plan to update the efficacy section of the alogliptin package insert with data from completed study MET-302. Since the efficacy information is not integrated, we agree with your plan to not include a Clinical Summary of Efficacy (2.7.3) in the resubmission.**

Question 9: Due to the fact that labeling negotiations had initiated under the previous review cycle and there are still some aspects other than safety that need to be discussed, Takeda proposes not to include Structured Product Labeling (SPL) in the NDA resubmissions. Takeda will provide the package insert information in SPL format once labeling language has been agreed upon by both Takeda and the Agency. Is this acceptable?

FDA Preliminary Response: Yes, your proposal is acceptable.

Question 10: Does the Agency agree with the process for enhanced monitoring of postmarketing liver-related cases?

FDA Preliminary Response: Yes, we agree with the process for enhanced monitoring of postmarketing liver-related cases.

Question 11: During the course of the review of the NDA resubmissions, spontaneous reports related to hepatic safety may be received. Takeda will continue to expedite these reports to the INDs and NDAs, as previously agreed. However, in an effort to provide a meaningful adjudication of these cases, Takeda often needs adequate time to gather relevant information for an individual postmarketing case. Therefore, the LSEC will review new cases on a monthly basis, and their assessments will be subsequently submitted to the Agency. Is this approach reasonable to the Agency?

FDA Preliminary Response: Yes, your approach is reasonable. However, additional information may be requested as needed.

Question 12: If during the course of the review of the NDA resubmissions, there is striking disagreement between the Agency and the LSEC on a particular liver safety case(s), would the Agency consider discussing the case(s) with the LSEC (and Takeda)?

FDA Preliminary Response: Yes, we may consider discussing case(s) with you and the LSEC. However, the purpose of such discussion would be to share information to ensure that both you and the Agency have all currently available data to aid decision-making. The

objective of the meeting would not be to obtain a consensus of opinion on liver case(s) or to discuss upcoming regulatory decision(s).

Question 13: Is the Agency agreeable to discussing how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End of Review meeting?

FDA Preliminary Response: Yes, we may discuss how to move forward with the SYR-322MET NDA at a meeting/teleconference to be held shortly after this End-of-Review meeting.

Question 14: In the 25 April 2012 Complete Response Letter, there are questions related to the alogliptin pediatric program. Takeda is currently planning on initiating the phase 3 program in early 2013 due to Pediatric Committee requirements. In order to incorporate the Agency's feedback into the studies before they are started, Takeda plans to submit responses to the pediatric questions in an IND Amendment. Is this proposal acceptable?

FDA Preliminary Response: You may submit responses to the pediatric questions in an IND amendment. However, please note that a pediatric postmarketing study requirement cannot be issued until after an NDA is approved. Please also submit relevant information to the NDA.

Additional Comment:
Please explain whether or not you plan to (b) (4) (b) (4) **could possibly offset the potential liver liability.**

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/s/

MEHREEN HAI
06/26/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jenipher E. Dalton
Interim Vice President, Quality Assurance
Takeda Global Research & Development
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Dalton:

Between November 28 and December 8, 2011, Ms. Kathleen S. Tormey, representing the Food and Drug Administration (FDA), conducted an investigation and met with your staff to review your conduct as sponsor of the following clinical investigations of the investigational drug Nesina (alogliptin):

> Protocol SYR-322_402, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment with Alogliptin in Addition to Standard of Care in Subjects with Type 2 Diabetes and Acute Coronary Syndrome," and
>
> Protocol 01-06-TL-322OPI-004, entitled "A Multicenter, Randomized, Double-Blind Study to Determine the Efficacy and Safety of the Addition of SYR-322 25 mg versus Dose Titration from 30 mg to 45 mg of ACTOS® Pioglitazone HCI in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Control on a Combination of Metformin and 30 mg of Pioglitazone HCl Therapy," and
>
> Protocol SYR-302_303, entitled "A Multicenter, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Alogliptin Compared to Glipizide in Elderly Subjects."

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Tormey during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Bldg. 51, Rm. 5328
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

JANICE K POHLMAN
05/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING REQUEST GRANTED

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to your correspondence dated April 27, 2012, requesting an End-of-Review meeting to discuss the deficiencies described in our Complete Response letter dated April 25, 2012, and to discuss actions to be taken to address these deficiencies. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	June 29, 2012
Time:	2:00 – 3:00 PM
Location:	10903 New Hampshire Avenue White Oak Building 22 Silver Spring, Maryland 20903

CDER participants (tentative):

<u>Office of New Drugs</u>

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Valerie Pratt, M.D.	Clinical Reviewer, DMEP

Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Biostatistics Reviewer, Division of Biometrics II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Eugenio Andraca-Carrera, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Amy Egan, M.D., M.P.H.	Deputy Director for Safety, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

Office of Surveillance and Epidemiology

Leonard Seeff, M.D.	Hepatologist
John Senior, M.D.	Hepatologist
Margarita Tossa, M.S.	Safety Regulatory Project Manager

Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mehreen Hai: x65073;
Lena Staunton: x67522.

Submit background information for the meeting (one electronic copy to the application and 25 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **May 30, 2012**, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

Mehreen Hai
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3391
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEHREEN HAI
05/09/2012

MEMORANDUM OF TELECON

DATE: **April 16, 2012 (12:00 – 1:00 P.M. EST)**

APPLICATION NUMBER: **Pending NDA 022271 and NDA 022426**

DRUG NAME: **Alogliptin tablets**
Alogliptin and pioglitazone fixed-dose combination tablets

BETWEEN:

Takeda Global Research and Development Center, Inc.
Sandra Cosner, RPh - Associate Director, Regulatory Affairs
Penny Fleck, MT - Senior Director, Clinical Science
Thomas Harris, RPh - Vice President, Regulatory Affairs
Qais Mekki, MD, PhD - Vice President, Pharmacovigilance
Azmi Nabulsi, MD - President, Takeda Global Research and Development
Neila Smith, MD - Executive Medical Director, Pharmacovigilance
Thomas Strack, MD - Therapeutic Area Head, Diabetes, Pharmaceutical Drug Development
Allison Villinski, MS - Director, Regulatory Affairs

External hepatology consultants for Takeda:

(b) (4)

AND

Office of New Drugs
Curtis Rosebraugh, MD - Director, Office of Drug Evaluation II
Mary Parks, MD - Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, MD, M.M.Sc. - Diabetes Team Leader, DMEP
Valerie Pratt, MD - Clinical Reviewer, DMEP
Mehreen Hai, PhD - Regulatory Project Manager, DMEP

Office of Surveillance and Epidemiology
Leonard Seeff, MD - Hepatologist
John Senior, MD - Hepatologist
Allen Brinker, MD, MS - Medical Team Leader, Division of Pharmacovigilance I (DPV I)
Margarita Tossa, MS - Safety Regulatory Project Manager

SUBJECT: Discussion regarding cases of hepatic injury associated with use of alogliptin

Background

Alogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that has been developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Alogliptin is a fourth-in-class new molecular entity. The NDA for alogliptin was submitted on December 27, 2007, and was issued a Complete Response letter on June 26, 2009. Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). The NDA for alogliptin-pioglitazone fixed-dose combination tablets was submitted on September 19, 2008, and was issued a Complete Response letter on September 2, 2009.

Takeda resubmitted both NDAs on July 25, 2011. On November 16, 2011, the review clock was extended by 3 months based on liver analyses submitted at our request, resulting in a PDUFA goal date of April 25, 2012.

During the review of the resubmissions, several pre- and post-marketing cases of liver injury associated with the use of alogliptin were identified. These cases were adjudicated to determine relatedness to alogliptin by the FDA hepatologists in the Office of Surveillance and Epidemiology, Dr. Leonard Seeff and Dr. John Senior, and also by Takeda's independent consultants, (b) (4).

While near-consensus was reached for most cases by these four hepatologists, one case in particular, TCI2011A04573, was adjudicated differently. This teleconference was arranged to allow discussion between the hepatologists regarding this case and, if needed, any additional cases.

Teleconference

After a brief introduction by Dr. Thomas Harris from Takeda, the four hepatologists discussed case TCI2011A04573. Dr. Seeff's opinion was that this case was probably related to the drug, while (b) (4) considered it unlikely to be drug-related, and (b) (4) considered it to be possibly related to the drug. (b) (4) considered this case to be more likely due to autoimmune hepatitis, noting the coexisting autoimmune thyroid disease and the rebound in the liver test elevations with tapering of the glucocorticoid dose. Dr. Seeff remained unconvinced given the negative autoimmune serologies and the development of liver injury coincident with the use of alogliptin. Dr. Joffe also questioned whether the rebound convincingly is related to the glucocorticoid taper as the liver tests improved despite a continued reduction in the glucocorticoid dose. There was also a brief discussion of six other cases: TCI2011A03640, TCI2010A05612, TCI2011A04039, TCI2011A06837, TCI2012A01179 and TCI2011A06481, with Dr. Seeff noting that he and (b) (4) are better aligned in their assessments for these cases than case TC2011A04573. At the end of the teleconference call, Dr. Parks stated that FDA is concerned with the signal for hepatotoxicity with alogliptin.

Memo prepared by: Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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MEHREEN HAI
04/26/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 3:18 PM
To: 'Cosner, Sandra (TGRD)'
Subject: RE: Info Request for NDA 22271 and 22426

Hi Sandy,
Please add the following two items to the information request below:

1. Clarify whether the patients who developed treatment-emergent ALT >10x ULN in the controlled phase 2/3 database all had ALT >3x ULN at baseline. What happened to ALT during the randomized treatment period for those with ALT >3x ULN at baseline?

2. At the teleconference call, we requested an estimate of patient-year exposures anticipated for Study 402 at the time 1.3 is met. When do you anticipate submitting this information?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 2:44 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info Request for NDA 22271 and 22426

Hi Sandy,
We have the following information request for the alogliptin NDAs:

Please refer to your November 7, 2011, response to our October 24, 2011, information request.

Table 7 in your November 7, 2011, submission (ongoing Study 402 alone) shows that 18 alogliptin-treated patients and 13 placebo-treated patients had a baseline ALT >3x ULN.
Table 8 in your November 7, 2011, submission (all completed phase 2/3 trials, including the Japanese phase 2/3 trials and ongoing Study 402) shows that 30 alogliptin-treated patients and 10 comparator-treated patients had a baseline ALT >3x ULN.

Please clarify the following:
1. Did all controlled phase 2/3 trials have ALT exclusion criteria except for Study 402? Were there any ALT exclusion criteria for the controlled phase 2/3 Japanese studies that were included in Table 8?
2. Clarify why the number of comparator-treated patients with baseline ALT >3x ULN is higher in Study 402 alone (n=13) compared to the pooled phase 2/3 database that includes Study 402 (n=10).
3. Did all the patients with baseline ALT >3x ULN in Tables 7 and 8 receive randomized study medication and have at least one post-baseline ALT value or do these tallies include some patients who were excluded from the trial?

Please respond as soon as possible.
Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
04/18/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Wednesday, April 18, 2012 2:44 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info Request for NDA 22271 and 22426

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Please clarify the following:
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2. Clarify why the number of comparator-treated patients with baseline ALT >3x ULN is higher in Study 402 alone (n=13) compared to the pooled phase 2/3 database that includes Study 402 (n=10).
3. Did all the patients with baseline ALT >3x ULN in Tables 7 and 8 receive randomized study medication and have at least one post-baseline ALT value or do these tallies include some patients who were excluded from the trial?

Please respond as soon as possible.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
04/18/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Monday, April 02, 2012 4:01 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info requests for NDA 22271 and 22416

Hi Sandy,
We have the following information requests for the alogliptin NDAs:

Regarding your cardiovascular trial (EXAMINE):

1. Have you completed enrollment in EXAMINE? Please provide 'n' for alogliptin and control who have had at least 6 months of exposure to treatment.
2. If answer to Q1 is 'no', how many patients have been randomized to alogliptin and control at present? How many of these have had at least 6 months of exposure to treatment?
3. If answer to Q1 is 'no', when do you anticipate completion of enrollment? And from this estimate, when do you anticipate all 5400 patients planned for study to have had at least 6 months of exposure to treatment?

Regarding the follow-up report that was submitted on March 30, 2012, for liver-related case TCI2012A01179:

4. The recent update for case TCI2012A01179 requires additional data to determine if the patient had acute hepatitis E infection. Please inquire of the reporting physician(s) whether there are stored, frozen serum samples available. We are specifically looking for HEV IgM and IgG antibodies. Serial tests of these antibodies and HEV RNA by PCR will be extremely useful.

5. Please also inquire of the reporting physician(s) whether an extensive history was taken of the patient's recent travels, exposure to animals or eating wild boar, and provide any such report.

Regarding liver-related case TCI2011A06481:

6. For postmarketing liver case TCI2011A06481, clarify whether there are hepatitis E test results available. If this patient did not undergo testing for hepatitis E, are there blood samples available that can be tested?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
04/02/2012

Hai, Mehreen

From	Hai, Mehreen
Sent	Friday, March 30, 2012 10:23 PM
To	'Cosner, Sandra (TGRD)'
Subject	RE: Info request for NDA 22271 and 22426

Sandy,
Thank you, we received your submission today.

We have the the following additional information requests for the alogliptin NDAs:

1. Have you been able to obtain any further information regarding postmarketing case TCI2011A06369?

2. Please provide us with the assessments from (b) (4) for postmarketing case TCI2011A06369 and TCI2011A06481. If these assessments have been previously submitted to the alogliptin NDA, please point us to their location.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Friday, March 30, 2012 1:15 PM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: RE: Info request for NDA 22271 and 22426

Hi Mehreen,
I wanted to give you a heads up that we are responding to this Information Request today. Please let me know if you would like for me to email you a copy in addition to the submission.
Thanks,
Sandy

Sandra D Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc
Office (224) 554-1957
Mobile (b) (6)
Fax (224) 554-7870
Email: sandra cosner@takeda com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs gov]
Sent: Tuesday, March 27, 2012 9:13 PM

To: Cosner, Sandra (TGRD)
Subject: Info request for NDA 22271 and 22426

Hi Sandy,
Please see below the information request for the alogliptin NDAs, that Dr. Parks mentioned during our conversation this afternoon, regarding the liver case that was reported in the safety report submitted on Thursday, March 22.

1. Please obtain medical/hospital records to determine if patient was ever febrile or complained of abdominal pain at presentation of this event.

2. Please obtain a complete report from the pathologist reading the liver biopsy results.

3. Please inquire if patient has been tested for Hepatitis E.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
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Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
03/30/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Tuesday, March 27, 2012 10:13 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info request for NDA 22271 and 22426

Hi Sandy,
Please see below the information request for the alogliptin NDAs, that Dr. Parks mentioned during our conversation this afternoon, regarding the liver case that was reported in the safety report submitted on Thursday, March 22.

1. Please obtain medical/hospital records to determine if patient was ever febrile or complained of abdominal pain at presentation of this event.

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3. Please inquire if patient has been tested for Hepatitis E.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
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Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
03/27/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Tuesday, March 20, 2012 11:03 AM
To: 'Cosner, Sandra (TGRD)'
Subject: Info request for NDA 22271

Hi Sandy,
We have the following information request for the alogliptin NDAs:

In your third Periodic Safety Update Report you state that the cumulative patient exposure to aloglipin (from approval through 15 October 2011) in the Japanese postmarketing setting is estimated to be 117,359 patient-years. The corresponding estimate for the alogliptin-pioglitazone fixed-dose combination product is 7,215 patient-years. Please clarify how you calculated these patient-year exposures.

Also, we had estimated that we would get our labeling comments back to you this week, but we will likely be delayed again to sometime next week, since our senior reviewers/management are currently engaged in internal discussion, and in the process of finalizing their reviews.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
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Ph: 301-796-5073
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/s/

MEHREEN HAI
03/20/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Thursday, March 15, 2012 10:13 AM
To: 'Cosner, Sandra (TGRD)'
Subject: Information requests for NDA 22271

Hi Sandy,
We have the following information requests for the alogliptin NDAs:

1. The narratives for the following liver cases contain insufficient information and some of them are poorly written with apparent discrepancies within the narrative. Please provide revised narratives that are thorough and clear. For each case that you do not attribute to alogliptin, state what you believe to be the alternative etiology:

OPI-002/831-2508
OPI-001/395-3054
012/961-3006
012/961-2501
TCI2011A02923 (insufficient information to determine whether the cause is hepatitis C or alogliptin-related hepatotoxicity).

2. In PSUR 3, the table with cumulative, unlisted serious adverse drug reactions shows one case of red blood cell aplasia. Please provide a narrative.

3. As of the May 31, 2011 cutoff date, clarify the extent of patient exposure in Study 012.

4. Provide narratives (or point us to the location within your submissions) for the alogliptin-treated patients in the Japanese phase 2/3 trials who discontinued due to drug hypersensitivity, dermatitis bullous, rash, toxic skin eruption and face oedema.

5. You table of treatment-emergent adverse events for the pool of phase 2/3 controlled studies shows that 5 patients reported a serious adverse event of pancreatitis. However, your table of narratives for pancreatitis show only 4 patients with serious pancreatitis. Please clarify the apparent discrepancy.

6. Please submit the narrative for the serious adverse event of drug hypersensitivity reported in an alogliptin-treated patient in your Japanese controlled phase 2/3 trial.

7. Please submit narratives for the alogliptin-treated patients in your phase 2/3 program (including Japanese studies and ongoing Study 402) who had adverse events that coded to the preferred terms of angioedema (n=1), face oedema (n=6), swelling face (n=3), swollen tongue (n=1), and tongue oedema (n=1).

8. Please submit narratives for the alogliptin-treated patients in your phase 2/3 program (including Japanese studies and ongoing Study 402) who had adverse events that coded to the preferred terms of dermatitis exfoliative and exfoliative rash.

Thanks!

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/s/

MEHREEN HAI
03/15/2012

Hai, Mehreen

From: Hai, Mehreen
Sent: Wednesday, March 07, 2012 3:58 PM
To: 'Cosner, Sandra (TGRD)'
Subject: Info request for NDA 22271

Hi Sandy,
We have the following request for the alogliptin NDA:

Based on your response to our March 1, 2012 information request, we note that the final report for the EXAMINE trial is targeted for July 2015. Based on the current number of patients enrolled, discontinuation rate, and event rates for this trial, can you provide an estimate as to when you anticipate 550 events to occur for the next planned interim analysis?

Thanks!

Mehreen Hai, Ph.D.
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/s/

MEHREEN HAI
03/07/2012

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)"
Subject: Info Requests for NDA 22271 and 22426
Date: Thursday, March 01, 2012 11:52:00 AM

Hi Sandy,
We have the following information requests related to the alogliptin and alogliptin-pioglitazone NDAs:

Clinical:

1) Please submit a summary of your planned studies and ongoing studies for alogliptin, together with their status and estimated completion dates.

2) Please submit the first PSUR for your alogliptin products approved in Japan.

Biopharmaceutics:

3) Your language of the proposed specification (b) (4) Q) of the labeled amount is dissolved in 15 minutes" needs to be clarified as "Q = (b) (4) of the labeled amount dissolved in 15 minute". (b) (4) and "Q "are not same.

4) What is the pH of your dissolution medium?

Thanks!

Mehreen Hai, Ph.D.
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MEHREEN HAI
03/01/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Labeling comments for NDA 22271 and 22426 - Round 2
Date:	Friday, February 17, 2012 8:27:00 PM
Attachments:	Nesina-PI-FDA EDITS-17February2012.doc OSENI-PI-FDA EDITS-17February2012.doc FDA Response to Takeda re. Section 13.1 (2-17-12).pdf

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Hi Sandy,
Please find attached our second round of edits to the package inserts (PI) for alogliptin and alogliptin-pioglitazone, incorporating comments from all disciplines. The edits to the alogliptin-pioglitazone PI are minimal, as we have focused on the alogliptin PI during this round. We have requested that you incorporate the relevant changes in the alogliptin PI to the alogliptin-pioglitazone PI as well. We remind you once again that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Once again, please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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 also find attached a document containing our response to your document explaining the rationale for your edits made in Paragraph 2 of Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), that you emailed me on February 9, 2012, along with your first round of edits to the alogliptin and alogliptin-pioglitazone package inserts.

We request that you respond with your edits and comments by **Monday, February 27, 2012**.
Please confirm receipt of this email, and let me know if you have any questions.
Thanks!

Mehreen Hai, Ph.D.
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FDA Response to Takeda's document explaining the rationale for the edits made in Paragraph 2 of Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), emailed by Sandra Cosner (Takeda) to Mehreen Hai (FDA) on February 9, 2012

The Division and the Executive CAC considered your arguments that no carcinogenic effect of alogliptin was observed in the two-year rat bioassay. We recognize that these arguments were made in the original study report from (b) (4) in 2007, which were reviewed by the Division and thoroughly discussed with the Executive CAC at that time. We disagreed then and we continue to disagree with the interpretation that the C-cell findings in rats, particularly in male rats, were a spurious finding and not related to alogliptin. Based on the multiple to clinical exposure of the NOAEL, we agree that the finding in rats does not pose a substantial carcinogenic risk to human subjects under conditions of clinical use. This is explicitly stated in the proposed label. However, statistically significant tumor findings in rodent bioassays are nevertheless described in drug labels and, when supportive data are available, the findings are put in context regarding the human relevance of the finding.

Specific responses to your arguments are as follows:

Takeda Comments 1 & 2:

- Statistical analyses of hyperplasia, adenoma, or carcinoma separately only showed significance in the incidence of adenomas in males at the mid-dose (400 mg/kg/day) and not at the high-dose (800 mg/kg/day).
- No statistical significance was noted in the combined incidence of hyperplasia, adenoma, and carcinoma.

FDA Response: Hyperplasia, adenoma, and carcinoma of thyroid C-cells are considered a continuum of histological changes with preneoplastic lesions often proceeding to benign and then occasionally to malignant neoplasms. Consistent with McConnell's publication (1986), the incidence of C-cell benign and malignant tumors are combined for statistical comparisons. Hyperplasia is excluded from analysis because this lesion is not a neoplasm and hyperplasia is not typically diagnosed when neoplasms are present in the same organ. Statistical analysis demonstrates that the combined incidence of C-cell adenoma and carcinoma increased at the mid and high doses of alogliptin in male rats with statistical significance by trend and pair-wise comparison. This outcome will not change.

Takeda Comment 3:

- The incidence of adenomas in the control group of this study was lower than that seen in the Historical Control (HC) data from the testing laboratory. And, although the percentage of thyroid c-cell adenomas in alogliptin-treated males was slightly higher than the HC, 16.7% and 18.3% (400 and 800 mg/kg/day, respectively) compared to 15.4%, the incidences were essentially equivalent (10/65 HC versus 10 or 11/60 alogliptin).

<u>FDA Response</u>: A dose response was evident in male animals across the dose range for the combined adenoma/carcinoma C-cell findings and, as you note, the incidence exceeded historical controls at the high dose. If the observed incidences were indeed random variation around a historical mean, the probability that a dose response is observed in the relevant endpoint is very low. The increased incidence in females dosed with alogliptin but without a clear dose-dependence may in fact reflect a plateau in response; however, because statistical significance was not evident in females, the Executive CAC recommended against including this finding in the drug label.

<u>Takeda comment 4</u>:

- The dose response for both adenomas and precursory hyperplastic lesions in the thyroid c-cell was weak.

<u>FDA Response</u>: See response to Comments 1, 2 & 3, above.

<u>Takeda comment 5</u>:

- There is no evidence of mutagenicity in any of the nonclinical assays with alogliptin.

<u>FDA Response</u>: We agree that genotoxicity is not relevant to this case. Rather, we interpret this finding as evidence of a non-genotoxic carcinogenic response to alogliptin. Findings of C-cell tumors in rats have been observed with direct acting GLP1 agonists, suggesting a biologically plausible mechanism for the effects observed with alogliptin, which indirectly increases GLP1.

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/s/

MEHREEN HAI
02/17/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Info request for NDA 022271 and 022426
Date:	Wednesday, February 15, 2012 12:06:00 PM

Hi Sandy,
We have the following information request for the alogliptin NDAs:

In the November 7, 2011 submission to NDAs 022271 and 022426, in the During Treatment column of Table 8, you list 2, 8, 11, and 21 All Alogliptin subjects with ALT > 20x, >10x, >8x, and >5x ULN, respectively, and 6 All Comparator subjects with ALT >5x or >8x ULN. Within 1 week, submit narratives for these cases that are sorted by the degree of ALT elevation and treatment group. Submit these narratives to NDAs 022271, 022426, and 203414.

Thanks!

Mehreen Hai, Ph.D.
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/s/

MEHREEN HAI
02/15/2012

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)"
Subject: Info request for NDA 022271
Date: Thursday, February 09, 2012 2:55:00 PM

Hi Sandy,
We have the following information request for the alogliptin NDA:

On page 6 of 11 of your November 17, 2011 submission to NDA 022271, you state that alogliptin subject 402/8364-001 had a serious event within the Anaphylactic Reaction SMQ. However, your list of serious adverse event narratives for study 402 describes a serious event of musculoskeletal pain (CIOMS Report TPG2010A00693) for this patient. Please clarify if subject 402/8364-001 had a serious event within the Anaphylactic Reaction SMQ. Please submit the appropriate narrative for that event.

Thanks!

Mehreen Hai, Ph.D.
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/s/

MEHREEN HAI
02/09/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Labeling comments for NDA 22271 and 22426
Date:	Thursday, January 26, 2012 3:18:00 PM
Attachments:	Nesina-PI-FDA EDITS-26January2012.doc (b) (4) PI-FDA EDITS-26January2012.doc

Hi Sandy,
Please find attached our first round of edits to the package inserts for alogliptin and alogliptin-pioglitazone, incorporating comments from CMC, Pharm/Tox, Statistics and Clinical Pharmacology. Clinical comments are still pending, and will be provided to you once the clinical review is complete. We remind you that we are sending you these labeling comments as per our previous discussions regarding the timeline for labeling, and that this does not reflect on the final regulatory decision for these applications.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits Takeda has made to our prior edits and (2) any new edits from Takeda 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 this round of labeling negotiations in the label. When you add a comment bubble, please state " Takeda response to FDA change or Takeda Comment." This will be useful for showing which edits come from FDA vs. which edits were from Takeda . 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 confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Thanks!

Mehreen Hai, Ph.D.
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77 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MEHREEN HAI
01/26/2012

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)"
Subject: Info request for alogliptin
Date: Friday, January 13, 2012 3:56:00 PM

Hi Sandy,
We have the following information request regarding the three liver-related safety reports that were submitted to IND 69707 (alogliptin), IND 73193 (alogliptin-pioglitazone) and IND 101628 (alogliptin-metformin) on January 10, 2012:

Please let us know when you expect to have additional details on these three cases. Please also have your liver experts review these cases and submit these cases (with follow-up/additional information), together with the assessment from your two liver experts, to the pending NDAs for these respective products. While the alogliptin NDA is under review, please also submit to the NDAs all future alogliptin liver events that would ordinarily come in only to the INDs.

Also, please submit to your NDAs the most recent PSUR for your alogliptin products approved in Japan.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
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MEHREEN HAI
01/13/2012

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Carton and container labels for Nesina
Date:	Wednesday, December 21, 2011 1:16:00 PM
Attachments:	CC label comments for Nesina.pdf

Hi Sandy,
Please find attached our comments and recommendations regarding the carton and container labels for Nesina.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
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A. Insert Labeling

The symbols '<' and '>' utilized throughout the labeling are dangerous symbols that appear on the List of Error-Prone Abbreviations, Symbols, and Dose Designations. These symbols are often mistaken and used as opposite of intended. As part of a national campaign to avoid the use of dangerous abbreviations and symbols, FDA agreed not to use such symbols in the approved labels and labeling of products. We recommend you replace all instances of the symbol '<' with the phrase "less than" and the symbol '>' with the phrase "greater than."

B. General Comments (All strengths)

1. The proprietary name, Nesina, is presented [redacted] (b) (4) To avoid selection errors, revise the appearance of the proprietary name so that it appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
2. Increase the visibility of the established name by increasing the size of the font.

C. Nesina Bottles (All strengths and sizes)

1. Decrease the prominence of the quantity statement so that the proprietary name, established name, and strength are more prominent.

D. Nesina Blister Label Samples (12.5 mg, 25 mg)

1. Include a statement which communicates that the blister pack is not child resistant and to keep out of reach of children.

E. Nesina Blister Carton Labeling (12.5 mg, 25 mg)

1. See comment D1 above.

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/s/

MEHREEN HAI
12/21/2011

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Info request for alogliptin NDAs
Date:	Tuesday, December 20, 2011 2:38:00 PM

Hi Sandy,
We have the following information request for the NDAs for alogliptin (22271) and alogliptin-metformin (203414):

In the pediatric population, you should evaluate the efficacy and safety of alogliptin as monotherapy and in combination with metformin. You can either conduct a single phase 3 efficacy and safety trial that has two strata (a monotherapy stratum and an add-on to metformin stratum) or you can conduct two separate trials (a monotherapy trial and a separate add-on to metformin trial). In addition, while your proposed primary efficacy endpoint at 6 months is acceptable, there should be a controlled extension period so that the total treatment period is 1 year for your phase 3 pediatric trial(s). These requests are consistent with what we have expected with other recently approved treatments for type 2 diabetes. Submit a revised proposal to us for your pediatric phase 3 program within 1 month.

Please also submit an updated pediatric plan for alogliptin/metformin FDC after you revise the alogliptin pediatric plan. This updated plan should clarify how the revised pediatric phase 3 program for the alogliptin NDA will satisfy PREA for the alo/met NDA.

Thanks, and please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
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/s/

MEHREEN HAI
12/20/2011

From:	Hai, Mehreen
To:	"Cosner, Sandra (TGRD)"
Subject:	Information request for alogliptin
Date:	Wednesday, December 14, 2011 12:04:00 PM
Attachments:	IR for NDA 22271.pdf

Hi Sandy,
Please find attached an information request for NDAs 22271 and 22426.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
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Information request concerning elderly study 303:

The inspection findings are pending for site #3018 (Lagrosa) involved in study SYR-322_303. Therefore, for this study, please analyze the following without site #3018 and complete the table below:

- HbA1c change from baseline at week 52 for A) FAS/LOCF; B) PPS/LOCF
- HbA1c ≤ 7.0 at week 52 for FAS/LOCF (responder analysis).

Please also calculate two-sided 95% CI's of the treatment arm comparisons and complete the table below. We are using Tables 11.b and 11.h from the clinical report for Study 303 as models for this table.

Study 303: HbA1c change from baseline at week 52

Analysis population Study week Treatment groups	N	Baseline mean (SD)	Adjusted mean change from baseline at endpoint ± SE[1]	Difference in adjusted mean change (95% CI) [1]	P-value
1. HbA1c change from baseline at week 52					
A. FAS/LOCF					
Alogliptin					
Glipizide					
B. PPS/LOCF					
Alogliptin					
Glipizide					
2. HbA1c ≤ 7.0; Week 52; FAS/LOCF					
		n (%)		Odds Ratio[2] (95% CI)	
Alogliptin					
Glipizide					

Notes:

[1] Analysis for HbA1c change from baseline: The adjusted mean change from baseline at week 26 and the difference in the adjusted mean change were estimated from the primary analysis of covariance model, with treatment, study schedule and geographic region as class variables, and baseline HbA1c as a covariate.

[2] Analysis for HbA1c ≤ 7.0: The logistic regression model included effects for treatment, geographic region, study schedule and baseline HbA1c.

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/s/

MEHREEN HAI
12/14/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: RE: Nov 16 Information Request for NDA 22-271
Date: Monday, December 05, 2011 12:47:29 PM

Sandy,
Thanks for the clarification.
To clarify something from our end, please submit (b) (4) report, and highlight where his assessment differs from (b) (4)

Thanks!

Mehreen Hai, Ph.D.
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From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Monday, December 05, 2011 10:22 AM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: RE: Nov 16 Information Request for NDA 22-271

Hi Mehreen,
I apologize for any confusion. When I had sent you the email on Thursday I was not aware we would receive (b) (4) report earlier than expected. Then we received it Friday morning and therefore submitted on that same day. This is the same submission I said we would submit the week of Dec. 12, again, sorry for the confusion.

We will work on your additional request below and get back to you soon.
Thanks,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Office (224) 554-1957
Mobile (b) (6)
Fax (224) 554-7870
Email: sandra.cosner@takeda.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, December 02, 2011 8:58 PM
To: Cosner, Sandra (TGRD)
Subject: RE: Nov 16 Information Request for NDA 22-271

Thanks, Sandy. I'm a bit confused - you say in your email below that you will be submitting (b) (4) evaluation around December 16. Is this different from what you submiited to the NDAs today?

Also, we request that you provide (b) (4) evaluation for the cases in which his conclusions differed from (b) (4) conclusions.

Mehreen Hai, Ph.D.

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Fax: 301-796-9712

From: Cosner, Sandra (TGRD) [mailto:sandra.cosner@takeda.com]
Sent: Thursday, December 01, 2011 11:11 AM
To: Hai, Mehreen
Cc: Cosner, Sandra (TGRD)
Subject: Nov 16 Information Request for NDA 22-271

Dear Mehreen-

I wanted to quickly follow up on the Agency's November 16th information request regarding the receipt of additional information requested from (b) (4) Since the Agency's request requires (b) (4) to evaluate information from the ongoing CV outcomes trial (Study 402; EXAMINE), Takeda has unblinded (b) (4) per internal Standard Operating Procedures. (b) (4) has received all of the unblinded information from the submission provided to the Agency on November 7th and is currently evaluating the data. Takeda expects to receive his expert opinion and submit it to the FDA by no later than the week of December 12th.

In the spirit of transparency, Takeda also wanted to inform the FDA that an additional hepatologist, (b) (4) received the serious, non-serious and post-marketing cases (and these only) in a blinded fashion following the Agency's October 24th request for information. Takeda has received (b) (4) evaluation of the blinded cases and this evaluation is generally aligned with the information included in Appendix 1 of (b) (4) review provided to FDA on November 7th. Takeda, therefore, is not planning on including this report in the mid-December submission. Takeda is also not requesting additional feedback from (b) (4) in an effort to minimize the number of individuals unblinded to alogliptin data, but is instead focusing on providing the Agency with (b) (4) overall interpretation per your request in an expedited fashion.

If you should have any questions please feel free to contact me. Thanks!

Kindest Regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Mobile (b) (6)
Fax (224) 554-3646
Email: scosner@tgrd.com

###
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return e-mail and destroy this communication and all copies thereof, including all attachments.

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MEHREEN HAI
12/05/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request
Date: Wednesday, November 16, 2011 2:43:24 PM

Hi Sandy,
We have the following information request for NDA 22271 and 22426:

In reference to the liver-related information that you submitted on November 7, 2011, and more specifically the External Consultant Review by [redacted] (b) (4) (Appendix 1), please make a concerted effort to obtain additional information on the hepatic cases that [redacted] (b) (4) said were missing important information. Please also provide from [redacted] (b) (4) an overall conclusion as to whether there is a concern for severe drug induced liver injury with alogliptin based on the available cases (unblinded and blinded) and the pattern of ALT elevation across the controlled phase 2/3 program as well as in Study 402.

Thank you!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
11/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

REVIEW EXTENSION – MAJOR AMENDMENT

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to the July 25, 2011, resubmissions of your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to our October 24, 2011, request that you conduct a comprehensive evaluation of liver-related adverse events that have occurred with alogliptin-containing products in your global clinical trial database and postmarketing setting. This information request was triggered by a postmarketing case of biochemical Hy's Law (TCI2011A04573) and numerical imbalances for alogliptin vs. comparator in serum alanine aminotransferase (ALT) elevations in your phase 2/3 program, particularly in your ongoing cardiovascular outcomes trial (Study 402).

On November 7, 2011, we received your response dated November 7, 2011, to this information request. We have determined that this 281-page response qualifies as a major amendment to your applications. Therefore, this is considered a solicited major amendment. We also note that the receipt date is within three months of the user fee goal date. 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 25, 2012**.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at 301-796-5073.

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/

MEHREEN HAI
11/16/2011

From: Hai, Mehreen
To: "scosner@tgrd.com";
Subject: Info request for alogliptin
Date: Tuesday, November 08, 2011 3:00:47 PM

Hi Sandy,
For the alogliptin NDA, can you please submit an amendment to your pediatric plan to include certification of the grounds for deferring the studies and evidence that studies will be conducted with due diligence and at the earliest possible time. I've included below an example of the deferral certification wording. You obviously don't need to follow it word for word.

Let me know if you have further questions.
Thanks!

Request for Deferral of Pediatric Studies
<<Name of company>> is requesting deferral of pediatric studies for <<NDA #>>. This application requests approval of <<name of drug product>> as an adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization. No pediatric data, therefore, have been included in this application in accordance with the provisions of 21 CFR 314.55.

In accordance with 21 CFR 314.55(b)(1) FDA may, at the request of an applicant, defer submission of some or all assessments of safety and effectiveness in pediatric patients until after approval of the drug product for use in adults. At the End-of-Phase 2 meeting, the sponsor proposed a deferral of submission of pediatric data with the initial application on grounds that pediatric studies should be delayed until adequate safety and effectiveness data have been collected in adults. This proposal was agreed by the Agency at the End of Phase 2 Meeting and the Agency's agreement was confirmed at the Type C meeting held on ....

<<Name of company>> certifies that pediatric studies are planned and will be conducted with due diligence. Specific details about planned pediatric studies have recently been submitted to … etc, etc.

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
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/s/

MEHREEN HAI
11/08/2011

Hai, Mehreen

From: Suggs, Courtney
Sent: Tuesday, November 08, 2011 12:27 PM
To: Pratt, Valerie; Joffe, Hylton; Hai, Mehreen
Cc: Taylor, Amy
Subject: RE: Alogliptin PeRC Date

I have confirmed with my Team Leader that Alogliptin does not need to return to PeRC.
Courtney

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Pratt, Valerie
Sent: Tuesday, November 08, 2011 9:04 AM
To: Suggs, Courtney; Joffe, Hylton; Hai, Mehreen; Pratt, Valerie
Subject: FW: Alogliptin PeRC Date

11/8/11

Dear Courtney,

Can you please confirm that the third change to the alogliptin peds program (i.e. studying alo in treatment naïve subjects [in addition to add-on to metformin]) does not require PeRC input?

I suspect it doesn't as it is consistent with other recent PeRC plans (e.g. linagliptin NDA 201-280).

Thanks,
Valerie

<< File: N201280LinaPeRC.doc >>

From: Joffe, Hylton
Sent: Monday, November 07, 2011 7:30 PM
To: Hai, Mehreen; Pratt, Valerie; Vaidyanathan, Jayabharathi; Chung, Sang
Subject: RE: Alogliptin PeRC Date

Thanks. Just to clarfiy - the third change is that we would like them to also study in treatment naïve patients in the trial [redacted] (b) (4) ..can we confirm that this does not require PeRC input.

From: Hai, Mehreen
Sent: Monday, November 07, 2011 2:56 PM
To: Joffe, Hylton; Pratt, Valerie; Vaidyanathan, Jayabharathi; Chung, Sang
Subject: FW: Alogliptin PeRC Date

Hylton and all,
The peds group has decided that we don't need to go back to PeRC for alogliptin after all.
Please see Courtney's email below.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Suggs, Courtney
Sent: Monday, November 07, 2011 10:41 AM
To: Hai, Mehreen
Cc: Taylor, Amy
Subject: Alogliptin PeRC Date

Hi Mehreen,

I think it has been decided that Alogliptin does not have to come back to PeRC as long as the only changes are the ages and the study duration from when it came in 2008.

Thanks,
Courtney

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for alogliptin
Date: Thursday, October 27, 2011 4:14:07 PM
Attachments: N22271 Info Request 10-27-11.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Please submit the following within 3 weeks after receiving this information request.

1. Please clarify the acute pancreatitis search method used in the August 24, 2011, Analysis of Similar Events Summary submitted to alogliptin IND 69,707. In addition, clarify why the Integrated Summary of Clinical Safety in your Complete Response for alogliptin describes seven cases of acute pancreatitis (narrow scope) in controlled trials whereas the August 24, 2011, IND submission describes six cases in completed, randomized, controlled trials. Did your August 24, 2011, IND submission include a search for reports of acute pancreatitis in your completed Japanese controlled clinical trials? If not, query your phase 2 and phase 3 Japanese trials for acute pancreatitis using the same approach that you used for acute pancreatitis in your Integrated Summary of Clinical Safety for the non-Japanese pooled phase 2 and phase 3 trials. Please provide narratives for all postmarketing events of acute pancreatitis and all serious events of acute pancreatitis from your phase 2 and phase 3 Japanese trials.

2. Please provide a search of the clinical trials included in your Complete Response (including your Japanese controlled clinical trials and your uncontrolled open-label study) and postmarketing safety database for serious and nonserious events of hypersensitivity reactions. For this analysis, use the following SMQs: Anaphylactic Reaction (all narrow search terms and those patients meeting the Anaphylactic Reaction SMQ algorithm), Angioedema (show results using narrow search terms separately to results using broad search terms), and Severe Cutaneous Adverse Reactions (show results using narrow search terms separately to results using broad search terms). For the controlled clinical trials (including the Japanese trials), please tally events by the following treatment groups: alogliptin 25 mg, all alogliptin, all active comparators, and placebo. Present these results for all events (serious + non-serious) as well as separately for serious and non-serious events. Include in the top row of each table the number and percentage of patients reporting at least 1 event. Show the results from each SMQ in separate tables. Using only the narrow search terms for the three SMQs, calculate the number and percentage of patients in each treatment group who reported at least one hypersensitivity event (i.e., anaphylactic reaction and/or angioedema and/or severe cutaneous reactions). Please submit narratives for all serious events identified (or direct us to their location in your Complete Response).

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/s/

MEHREEN HAI
10/27/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for NDA 22271
Date: Monday, October 24, 2011 3:11:25 PM
Attachments: NDA 22271 and NDA 22426 IR.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

We are interested in obtaining more comprehensive, updated information regarding any potential cases of drug-induced hepatotoxicity in your global clinical trial and postmarketing database for alogliptin.

Please submit your response to the following within **2 weeks** of receiving this information request.

1. Query your global clinical trial database for cases of serious liver-related adverse events (including the need for liver transplantation or death) reported in alogliptin-treated patients or in patients who are still on blinded study medication. Provide detailed narratives for any cases that were not included in your NDA submission or resubmission.
2. In your NDA resubmission, you provide a Periodic Safety Update Report for alogliptin that contains a line listing of several postmarketing liver-related adverse events, such as non-serious adverse events of “Hepatic Function Abnormal” and “Liver Disorder”. We could not locate narratives for these potential adverse events of interest. Re-query your global postmarketing database for serious and non-serious cases of liver-related adverse events. Provide detailed narratives for all identified cases.
3. Query your global clinical trial and postmarketing database for cases meeting the biochemical definition of Hy's Law (ALT > 3x ULN and total bilirubin > 2x ULN). Provide detailed narratives for those cases that were not included in your NDA submission or resubmission.
4. In your NDA resubmission, the interim results from Study 402 show a numerical imbalance not favoring alogliptin with regard to the percentage of patients with serum ALT >3x ULN, >5x ULN, and >8x ULN. Re-analyze these liver data using updated data from this trial (ensure that this analysis is adequately firewalled so as not to impact integrity of the ongoing study). For this new analysis, also include ALT >10x ULN and ALT >20x ULN.
5. Provide an updated analysis showing the number and percentage of individuals with serum ALT >3x ULN, ALT>5x ULN, ALT>10x ULN, and ALT>20x ULN based on all of your completed, controlled, phase 2 and phase 3 clinical studies to date. Include updated data from Study 402. Include data from your IND and non-IND studies (e.g., include data from the studies conducted for the Japanese regulatory authorities). Show these data for each alogliptin dose and for each comparator as well as for all alogliptin dose groups combined and all comparators combined. Include an analysis that accounts for patient-year exposure. Provide detailed narratives for those cases with serum ALT >5x ULN that were not included in your NDA submission or resubmission.

For requests 1-3 above, your searches for cases should include all available sources (e.g., spontaneous reports, post-marketing studies, completed or ongoing clinical studies) and should include patients who are on blinded study medication. Include cases involving any individual who has ever taken alogliptin for any duration, either alone or in combination with other medications (including as a fixed-dose combination). The source of the data

should be clearly indicated. Be sure to list the specific databases you queried and include the search strategy.

Include all cases (whether or not they were adjudicated) regardless of the reporters', investigators', or sponsor's attribution of causality—even if you believe there are potential confounders or plausible alternative etiologies.

Include data from all sponsored (whether or not they were designated as IND studies) and non-sponsored clinical studies.

Include updated information regarding the estimated number of patients for whom alogliptin products have been prescribed in the countries where these products are approved.

Include information on the number of patients treated with alogliptin products and comparators in your clinical trials database, including data on duration of exposure and alogliptin dose.

Please submit the requested information to both the alogliptin and alogliptin/pioglitazone FDC NDAs.

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MEHREEN HAI
10/24/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Information request for NDA 22271
Date: Tuesday, September 27, 2011 2:09:47 PM
Attachments: Alo IR.pdf

Hi Sandy,
Please find attached an information request for NDA 22271 and 22426.
Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

For Study SYR-322_301, the inclusion criteria include apolipoprotein E 3/3 or apolipoprotein E 3/4 phenotype positivity prior to baseline. Please clarify why this was a required inclusion criterion and how it impacts generalizability of results to the overall type 2 diabetes population.

For Study SYR-322_303:

1. Please complete the following table.

2. Please run the following sensitivity analyses using the same methodology that was used for the primary efficacy analysis. Each analysis should be performed using both the FAS (using LOCF after rescue) and PPS:

Analysis 1: For the glipizide arm, only include patients who reached a final glipizide dose of 10 mg daily.

Analysis 2: For the glipizide arm, only include patients who either reached a final glipizide dose of 10 mg daily or who were downtitrated from 10 mg due to hypoglycemia.

3. For glipizide, the maximum recommended total daily dose is 40 mg. Clarify why you limited the glipizide dose to only 10 mg daily, particularly if patients did not achieve adequate glycemic control on this dose.

	Number / %
I. Glipizide arm (+ alogliptin placebo)	
A. Received at least one dose of glipizide 5 mg	
1. Not uptitrated	
a. Not rescued	
i. Completed the study	
ii. Discontinued the study	
b. Was rescued (after week 12)	
2. Uptitrated to glipizide 10 mg (sometime in weeks 1-12)	
a. Not downtitrated	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
b. Downtitrated (any time from uptitration week through week 52)	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
B. Did not receive at least one dose of glipizide 5 mg (these subjects are not in the FAS?)	
II. Alogliptin arm (+ glipizide placebo)	
A. Received at least one dose of glipizide placebo 5 mg	
1. Not uptitrated	
a. Not rescued	
i. Completed the study	
ii. Discontinued the study	
b. Rescued (after week 12)	
2. Uptitrated to glipizide placebo 10 mg (sometime in weeks 1-12)	
a. Not downtitrated	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
b. Downtitrated (any time from uptitration week through week 52)	
i. Not rescued	
- Completed the study	
- Discontinued the study	
ii. Rescued	
B. Did not receive at least one dose of glipizide placebo 5 mg (these subjects are not in the FAS?)	

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/s/

MEHREEN HAI
09/27/2011

From: Hai, Mehreen
To: Cosner, Sandra (TGRD);
Subject: Info request
Date: Tuesday, September 20, 2011 2:17:37 PM

Hi Sandy,
Got your voicemail from earlier today. I'm working from home today, but I'm happy to talk tomorrow, if you like. We don't need anything further for the pediatric plan/history, or the REMS. Regarding the inspections, that is handled by the Office of Scientific Investigations. If there are any further inspections to be done, they will get in touch with you in a timely manner, but if you still have questions, I can find out who you need to contact in OSI.

In the meantime, we have the following information request, related to the site inspections:

For studies 303 and OPI-004, were all subjects who were discontinued due to lack of efficacy actually rescued from hyperglycemia? Were there any subjects who were rescued from hyperglycemia who were not classified as having been discontinued due to lack of efficacy? Provide a list of rescued subjects by study site for these trials. Also provide a list of subjects who were discontinued due to lack of efficacy by study site for these trials.

Please provide a response at your earliest convenience.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
09/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).[1] The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

[1] These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDAs. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

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/

JULIE C MARCHICK
09/07/2011
J. Marchick signing for M. Parks

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

ACKNOWLEDGE – CLASS 2 RESPONSE INFORMATION REQUEST

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

We acknowledge receipt on July 25, 2011, of your July 25, 2011, resubmissions of your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We consider these to be complete, class 2 responses to our action letters dated June 26, 2009 (for alogliptin) and September 2, 2009 (for alogliptin-pioglitazone fixed-dose combination). Therefore, the user fee goal date for both NDAs is **January 25, 2011**.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

1. Tables 8.4.2.6Ra, 8.4.2.7Ra, 8.4.2.8Ra, and 8.4.2.9Ra in the Integrated Analysis of Safety show adverse events by renal function (estimated using Cockcroft-Gault and MDRD formulas) for your controlled phase 2/3 trials. To facilitate our review, please submit revised tables presenting these data as follows:
   - Show only n (%) for each treatment group so that, for a given preferred term (PT), all treatment groups fit on one page.
   - Show results by System Organ Class and PT, but include only those PTs reported in >2% of all alogliptin-treated patients.

2. Figure 1 in the alogliptin NDA shows a graphical display of when the first primary MACE composite event occurred relative to the index acute coronary syndrome (ACS) event in cardiovascular study SYR-322_402. Please also submit the previously requested subgroup analysis evaluating the primary and secondary endpoints according to subjects with an index ACS event ≤2 months vs. >2 months prior to randomization.

3. For the alogliptin NDA, there are 36 subjects who were randomized to study SYR-322 402 and appear in the dataset *D mace* for SYR-322 402 located in Section 5.3.5.1.21.1.1, but do not appear in the dataset *D mace*, combined across studies, in Section 5.3.5.3.25.1.1. Please clarify why these subjects do not appear in the combined dataset.

4. Submit an updated pediatric development plan for both NDAs that addresses our comments from the End-of-Review meeting held on February 23, 2010. This plan should include your currently proposed ages for waiver and deferral requests together with supporting rationale. For those pediatric studies you wish to defer, provide synopses as well as a timeline for completion of the studies (this should include the date by when the final protocols will be submitted, the date by when the studies will be completed, and the data by when the complete study reports will be submitted to FDA). When determining a date for final protocol submission, you should ensure that there is sufficient time to allow FDA feedback on your draft protocols (the protocol will only be considered final after FDA agrees with the study design). We recommend that you request a full waiver for the alogliptin-pioglitazone fixed-dose combination tablet because of safety concerns with use of pioglitazone in children (e.g., risk of bladder cancer, bone effects).

5. Clarify whether there are other completed or ongoing Phase 3 studies with alogliptin or alogliptin-pioglitazone fixed-dose combination tablets that were not included in the resubmissions.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at 301-796-5073.

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
08/15/2011

Marchick, Julie

From: Marchick, Julie
Sent: Thursday, July 28, 2011 10:53 AM
To: 'allison.villinski@tgrd.com'; 'scosner@tgrd.com'
Cc: Hai, Mehreen
Subject: NDA 22271 and NDA 22426 Alogliptin and Alogliptin/Pioglitazone - Information Request

Good Morning Allison and Sandy,

We have the following requests. Please let us know when you anticipate you will be able to submit this information.

1. In the preliminary minutes for our June 20, 2011 meeting, we provided a list of the information needed to determine which clinical site inspections will be conducted for EXAMINE. We could not find this information in the NDA submission. Please clarify where this information is located in the NDA submission. If it is not in the NDA, please submit the information. At a minimum, we need the following information for Study 402 as soon as possible to start the inspection process:
(A) a listing by site of the number of patients screened, enrolled and discontinued,
(B) a listing of the contact information for each site. You may model your response on that found under Module 5.3.5.1.7 for Study SYR-322-303 in your Alogliptin submission.

2. Please submit an updated pediatric development plan with timelines for NDAs 22-271 and 22-426. This plan should include your currently proposed ages for waiver and deferral requests together with supporting rationale. For those pediatric studies you wish to defer, provide synopses as well as a timeline for completion of the studies (this should include the date when the final protocols will be submitted, the date when the studies will be completed, and the data when the complete study reports will be submitted to FDA). When determining a date for final protocol submission, you should ensure that there is sufficient time to allow FDA feedback on your draft protocols (the protocol will only be considered final after FDA agrees with the study design).

Thanks,
Julie

Julie Marchick
Acting Chief, Regulatory Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

JULIE C MARCHICK
07/28/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Response to your questions
Date: Wednesday, July 20, 2011 4:51:51 PM

Hi Sandy,
In response to the two questions you asked me on Monday:

1) Regarding the information we need for the clinical site inspections, please provide only the following info for each of the other Phase 3 trials that you plan to include in the NDA resubmission, in a tabular format by site.

a. Number of subjects screened for each site by site
b. Number of subjects randomized for each site by site
c. Number of subjects treated who prematurely discontinued for each site by site

Please try to include this information in the NDA resubmission. Also, in response to your voicemail this morning, please also include this information for the studies that have been inspected previously, since that is likely to have been a while ago. You can mention in your submission that they were previously inspected.

2) Regarding the response to our Biopharm comment, you may respond to our comment after resubmission of the NDA. However, it will be better if you can send us a concurrence as soon as possible about whether or not you agree to our request so that you can update your ongoing stability program based on our proposed specification. Also, if you have samples taken as per our recommendation, you need to submit them as soon as possible. But none of this should hold up your NDA resubmission.

Please let me know if this is not clear.
I'm working from home today, so please email me if you need further clarification.

Mehreen Hai, Ph.D.
Regulatory Project Manager
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/s/

MEHREEN HAI
07/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin-pioglitazone fixed-dose combination tablets.

We also refer to the teleconference between representatives of your firm and the FDA on June 20, 2011. The purpose of the meeting was to discuss the upcoming re-submissions of the referenced NDAs in response to our Complete Response letters dated June 26, 2009 (alogliptin) and September 2, 2009 (alogliptin and pioglitazone fixed-dose combination).

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	Monday, June 20, 2011, 1:00 – 2:00 PM (Eastern)
Meeting Location:	Teleconference
Application Number:	NDA 022271 and NDA 022426
Product Name:	Alogliptin tablets Alogliptin and pioglitazone fixed-dose combination tablets
Indication:	Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Hylton Joffe, MD, MMSc
Meeting Recorder:	Mehreen Hai, PhD

FDA ATTENDEES

Mary Parks, MD	Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, MD, MMSc	Diabetes Clinical Team Leader, DMEP
Ilan Irony, MD	Diabetes Clinical Team Leader, DMEP
Valerie Pratt, MD	Clinical Reviewer, DMEP
Eugenio Andraca-Carrera, PhD	Statistics Reviewer, Division of Biometrics VII
Todd Sahlroot, PhD	Deputy Director, Division of Biometrics II
Janice Derr, PhD	Statistics Reviewer, Division of Biometrics II
Julie Marchick, MPH	Acting Chief, Project Management Staff, DMEP
Mehreen Hai, PhD	Regulatory Project Manager, DMEP
Susan Leibenhaut, MD	Medical Officer, Division of Scientific Investigations

SPONSOR ATTENDEES

Sandra Cosner, RPh	Associate Director, Regulatory Affairs
Penny Fleck, MT	Director, Clinical Science
Thomas Harris, RPh	Vice President, Regulatory Affairs
Mick Roebel, PhD	Senior Director, Regulatory Affairs
Nancy Siepman, PhD	Vice President, Analytical Science
Thomas Strack, MD	Vice President, Clinical Science
Allison Villinski, MS	Director, Regulatory Affairs
Craig Wilson, PhD	Principal Statistician, Biostatistics

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for the alogliptin-pioglitazone fixed-dose combination tablet on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist approved by FDA on July 15, 1999, under NDA 021073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009, for NDA 022426.

Takeda intends to resubmit these two NDAs in July 2011. The purpose of this meeting was to discuss the upcoming resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426, and to address particular aspects of the ongoing cardiovascular outcomes trial (EXAMINE) for alogliptin.

2. DISCUSSION

Your questions are repeated below in plain font. Our preliminary responses sent to you on June 17, 2011, follow in bold font. A summary of the meeting discussion is shown in italic bold font. Post-meeting comments are shown in underlined plain font.

Question 1:

As has been discussed previously with the Division, Takeda has established appropriate firewalls to ensure that the ongoing conduct of EXAMINE is being performed by individuals who have not been made aware of the results from the interim analysis. Based on the outcome of the Agency's review, EXAMINE could be ongoing at the time of the Agency's approval of alogliptin.

Has the Agency considered how the integrity of the double blind study will be maintained after approval in light of the Freedom of Information Act (FOI) (e.g. redaction of the EXAMINE interim analysis results in reviews posted on the Drugs@FDA website)?

FDA Preliminary Response: Yes. Interim results from ongoing cardiovascular outcomes trials for anti-diabetic medications will be redacted from FDA's clinical and statistical reviews prior to posting of these reviews on the FDA website. In addition, these interim results will not be included in the approved package insert.

Meeting Discussion: Takeda clarified that all of its personnel present at this teleconference call have already been unblinded to the interim results of EXAMINE.

FDA confirmed that we will redact portions of our reviews that discuss interim results from EXAMINE before the reviews are posted publicly. As an additional safeguard, FDA recommended that Takeda clearly identify in their resubmission all data that are derived from interim analyses of EXAMINE that should not be disclosed in public FDA reviews. Takeda offered to read FDA reviews to help identify any data that should be kept confidential but FDA

explained that our policy is not to share our reviews with anyone outside FDA prior to the public posting.

Question 2:

During the Post-Action Feedback meeting with the Agency on January 12, 2010 and the End-of-Review meeting held on February 23, 2010, Takeda stressed its high level of commitment to submitting complete and high quality re-submissions for the alogliptin and alogliptin/pioglitazone FDC. In addition, Takeda emphasized the need for timely communications, transparency and review efficiencies within the Agency following the re-submissions. To that end, Takeda would like the Agency to re-confirm the following:

a) The user fee goal date for a re-submission is 6 months from receipt of the amendment to the NDA. If the alogliptin and alogliptin/pioglitazone FDC re-submissions are provided to the Agency at the same time, they will be on the same review clock and have the same user fee goal date.

FDA Preliminary Response: Yes, that is correct.

Meeting Discussion: There was no discussion of this response.

b) Labeling discussions will begin at least 4 weeks prior to the scheduled action dates should the data from the application support approval.

FDA Preliminary Response: Yes, that is correct.

Meeting Discussion: There was no discussion of this response.

c) The proposed tradenames for alogliptin and alogliptin/pioglitazone FDC (Nesina and (b) (4) respectively) will be reviewed within 90 days of the NDA re-submissions.

FDA Preliminary Response: Yes, that is correct. Please refer to the Guidance for Industry entitled *Contents of a Complete Submission for the Evaluation of Proprietary Names* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf).

Meeting Discussion: Takeda raised additional questions about the tradename review process, such as concurrent submission of other tradenames in case the currently proposed tradenames are found unacceptable. FDA recommended that Takeda follow the guidance mentioned above and that, if there are any remaining questions, that those questions be submitted for review by the Division of Medication Error Prevention and Analysis (DMEPA).

d) In general, the re-submission review timelines will be communicated to the Sponsor so that Takeda can promptly provide responses to the Agency's requests, ensuring efficiency of the overall review process.

FDA Preliminary Response: We will establish internal timelines to ensure timely review of your re-submissions within the 6-month review clock. Early in the review process, we will inform you of when we expect to communicate proposed labeling and, if necessary, any requests for postmarketing commitments or postmarketing requirements. If we have information requests during our review we will send these to you as soon as they are identified.

Meeting Discussion: There was no discussion of this response.

e) Does the Agency anticipate conducting clinical site inspection(s) based on the additional studies included in the re-submission? If so, what is the timing with respect to the review clock for the conduct and completion of the site inspection(s)?

FDA Preliminary Response: A determination of whether or not clinical site inspections need to be conducted will be made at the time of NDA re-submission. Because of the short timeline, in order for us to efficiently prepare for inspections, we request that the information in the attached documents be submitted at the time of the submission of the application.

Meeting Discussion: Takeda clarified that it will provide this information.

Post-Meeting Comment: Given your intent to submit other Phase 3 trial reports with EXAMINE (e.g. elderly study report and trials with pioglitazone), please include the above requested information for those trials as well.

f) Although no new Chemistry, Manufacturing and Controls (CMC) information will be included in the re-submissions, does the Agency anticipate conducting Prior Approval Inspections (PAIs) of the manufacturing facilities?

FDA Preliminary Response: Yes, we may decide to conduct a PAI. Form FDA 356h of the resubmissions should include all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and a statement that they are immediately ready for GMP-inspection.

Meeting Discussion: There was no discussion of this response.

g) Can the Agency confirm that if the issues cited in the Complete Response Letter have been adequately addressed and no further issues are identified during the review, an Advisory Committee meeting would not be necessary?

FDA Preliminary Response: An advisory committee (AC) meeting will likely not be needed if we determine that you definitively address the deficiencies in the Complete Response letter and we do not identify any unexpected efficacy or safety findings during our review. A final determination of whether or not an AC meeting will be required will be made after NDA re-submission.

Meeting Discussion: There was no discussion of this response.

Question 3:

Takeda would like to propose language to be included in the prescribing information (e.g. under Adverse Reactions) with the available cardiovascular safety data on alogliptin. (b) (4)

While Takeda recognizes that the Agency cannot comment on specific labeling language at this time, will the Agency consider Takeda's proposal to provide physicians cardiovascular safety information based on a meta-analyses that includes integration of the EXAMINE interim data?

FDA Preliminary Response: No. FDA is not permitting cardiovascular outcomes data that meet the 1.8 cutpoint in approved labeling, regardless of whether these data are derived from completed or ongoing trials. Approval of a new treatment for type 2 diabetes implies that the 1.8 cutpoint has been met because our Guidance states that this cutpoint must be met to support approval. Please also see our response to Question 1.

Please also respond to the following questions:

1. **Question 3 states** (b) (4)
   Please clarify to which (b) (4) **you are referring.**
2. **What is the status of the EXAMINE study with respect to the pre-specified group sequential procedure corresponding to the 1.8 hazard ratio non-inferiority margin? The procedure specifies interim analyses at 80, 100, and 125 adjudicated primary MACE events and a final analysis at 150 events. We would like to know the total number of adjudicated primary events in the MACE composite in EXAMINE that were analyzed and used as the basis of the decision to re-submit the NDA. We would also like to confirm (yes or no) that the test statistic for this analysis satisfied the group sequential boundary. However, until the time the NDA is re-submitted, we would like to remain blinded to the number of events in each treatment arm and to the value of the test statistic.**
3. **What is the anticipated number of patients with at least one year of exposure to study drug in the EXAMINE trial at the time of NDA resubmission? What is the anticipated mean exposure for the trial?**
4. **Clarify what else you are planning to include in the NDA resubmission besides the interim results from EXAMINE.**

***Meeting Discussion*: Takeda asked if selected information from the interim results for EXAMINE (e.g., patient demographics) could be included in labeling. FDA stated that Takeda should include the proposed labeling with the resubmission, together with rationale for data they would like to include from EXAMINE. A final decision will be made after FDA has reviewed the resubmission.**

Follow up discussion of Sub-Question 1: Takeda stated that they will submit a MACE analysis (death, myocardial infarction, and stroke) based on the interim data from the EXAMINE trial alone as well as a meta-analysis of the interim results from EXAMINE together with the completed Phase 2/3 trials. FDA stated that this is acceptable but that, as discussed on April 27, 2009, the EXAMINE trial must be able to stand alone for addressing cardiovascular (CV) safety for alogliptin.

Follow up discussion of Sub-Question 2: Takeda said it achieved the 1.8 non-inferiority margin with (b) (4) events of death, myocardial infarction, and stroke. Takeda used an alpha of 0.002 consistent with the pre-specified group sequential test at the first interim analysis scheduled for 80 events. FDA thanked Takeda for providing this information.

Follow up discussion of Sub-Question 3: Takeda stated that the resubmission will contain data on 526 patients (400 patients combined in trials 1 and 2 below; 100 patients in EXAMINE) exposed to alogliptin for >1 year in the following three new trials:

1. ***Alogliptin versus pioglitazone trial***
2. ***Alogliptin versus sulfonylurea trial in the elderly***
3. ***EXAMINE trial: Approximately 100 patients per treatment arm with >1 year exposure to study medication with a mean exposure of 5-6 months. This trial is still enrolling.***

Follow up discussion of Sub-Question 4: Takeda plans to submit the following new trials: EXAMINE, two Phase 3 studies, two Phase 1 studies, Japanese (safety) studies, and non-clinical data, as per discussions at the February 23, 2010, End-of-Review meeting. No Chemistry/Manufacturing/Controls (CMC) information will be submitted.

FDA asked Takeda to clarify its pooling strategy for the new Phase 3 trials. Takeda stated that the safety analysis will be similar to that discussed at the February 2010 End-of-Review meeting. The safety data will be pooled with and without EXAMINE. Old versus new data will be highlighted. Changes in the incidence of adverse events and serious adverse events between the initial submission and resubmission will be discussed. FDA asked Takeda to send in a synopsis of how the Phase 2/3 data will be presented in the planned NDA resubmission. Takeda agreed and clarified that the goal NDA resubmission date for both NDAs is July 25, 2011.

Post-Meeting Comment: Takeda provided the table of contents for the proposed resubmissions by email on July 8, 2011, but this document does not explicitly state how the data will be presented. Takeda should specifically clarify if there are any deviations from agreements reached at the End-of-Review meeting regarding content and data presentation for the resubmissions.

Question 4:

As per Takeda's agreement with the Agency, Takeda is planning on continuing the EXAMINE trial until the protocol planned final analysis. However, the Data Monitoring Committee (DMC) has recently requested guidance on how to proceed with reviewing the cardiovascular safety data from the ongoing EXAMINE trial should the MACE hazard be [redacted] (b) (4) (b) (4) akeda would like to discuss guidance that can be given to the DMC to ensure that the study is not stopped until the study has [redacted] (b) (4) Following the NDA re-submissions, Takeda plans to submit a meeting request to discuss this topic further.

Does the Agency agree with Takeda's proposal?

FDA Preliminary Response: Based upon information submitted in your briefing jacket, it is unclear how a [redacted] (b) (4) would be incorporated into your protocol. Based on the pre-specified statistical plan for assessing the 1.3 margin, it appears that you will not [redacted] (b) (4) More detailed information on your proposed changes to the study design and stopping rules is needed in order to evaluate your proposal. With that being said, the following are some points to consider.

[redacted] (b) (4) **Please, therefore, submit your meeting request to discuss this topic prior to NDA resubmission and our review of the data.**

[redacted] (b) (4) **Adequate statistical and operational justification should be provided for any proposed changes, including details on the alpha-spending function and power. If previously submitted simulations are no longer representative of the modified trial, a new set of simulations may be required. All proposed changes should also be discussed and approved by the DMC to ensure they are in the best interest of the patients. If at some point the DMC recommends prematurely stopping EXAMINE, we recommend that you notify FDA before stopping the trial.**

***Meeting Discussion**: Takeda agreed to submit a Type B meeting request to discuss this issue prior to NDA resubmission and asked for an expedited review and meeting date. FDA responded that we will do our best to accommodate the requested timeline but cannot guarantee that we could do so. Takeda replied that it will propose an analysis plan for* [redacted] (b) (4)

FDA followed up on Takeda's initial statement that all of its teleconference participants were unblinded to the study results. FDA asked who from Takeda will be writing the revised plan (b) (4) Takeda replied that they had planned to have the unblinded team do so. FDA responded that our goal is to be as objective as possible when reviewing the statistical analysis plan by remaining blinded to study results and that Takeda should do the same. Takeda agreed to do so.

Post-Meeting Comment:

On June 22, 2011, FDA sent the following email to Takeda:

"During the June 20th, 2011 teleconference with the Agency to discuss NDA 022271 and NDA 022426, Takeda discussed the first interim analysis of the EXAMINE trial. The first interim analysis was conducted according to the pre-specified plan after (b) (4) MACE events have been observed in EXAMINE. According to Takeda, the results of this interim analysis achieved the 1.8 non-inferiority margin for the relative risk of MACE. The EXAMINE protocol states that the next interim analysis will test for a non-inferiority margin of 1.3 after 550 events have been observed. Takeda discussed their wish to deviate from the original EXAMINE protocol to allow for an interim analysis for non-inferiority, (b) (4) The timing proposed for this additional interim analysis, in terms of number of events, was not discussed during the teleconference.

In general, data driven changes in the timing of interim analyses present a challenge and are to be avoided. It is often difficult or impossible to evaluate the statistical properties of tests conducted at these data driven interim looks. Both Takeda and the Agency should try to be as objective as possible when writing and reviewing proposed changes to a statistical analysis plan. In the case of the EXAMINE trial, it is known that the noninferiority margin of 1.8 was met at (b) (4) events. This information sets a bound for the observed relative risk of MACE at (b) (4) events. Therefore all additional, not previously planned, interim analyses in EXAMINE are unblinded to the available data.

During the teleconference, the Agency agreed to further discuss Takeda's proposal. We recommend that you consider that any additional interim analyses in the EXAMINE trial should maintain the Type I error for noninferiority, and should minimize the potential bias resulting from knowing the results of the first interim analysis. The following two approaches meet these criteria; you may propose other approaches as long as they maintain Type I error and minimize bias:

1) Use of a Peto-type stopping rule. This approach spends a very low alpha at each interim look and allows for an unspecified number of interim looks.
2) Consider using the first (b) (4) events in the EXAMINE trial as a pilot study from which to estimate the statistical characteristics of the remainder of the study. The results of the additional proposed interim analysis at n events would be based only on the last n- (b) (4) events.

We also would like to remind Takeda of our interest, as part of the complete response submission, in a subgroup analysis that evaluates the primary and secondary endpoints of the

EXAMINE study, according to subjects with an ACS event < 2 months versus subjects with an ACS event > 2 months prior to randomization."

Takeda responded on June 28, 2011 by email stating:

"Thank you again for the informative teleconference that was held with the Division on June 20th as well as the e-mail communication regarding the ongoing cardiovascular outcomes trial (Study 402, EXAMINE) sent on June 22nd. Based on the feedback that Takeda has received from the Agency and internal discussions, Takeda has decided not to make any revisions to the protocol or Statistical Analysis Plan (SAP) for EXAMINE.

However, as noted in the June 20th teleconference, Takeda is looking for clarification from the Agency on the requirements needed to (b) (4) (b) (4)

Although we are no longer planning to modify the statistical plan, we remain concerned that it is the DMC's desire to request their own analysis of the primary endpoint prior to the next interim look at 550 events and recommend the study stop early on the basis of preserving subject safety for those randomized (b) (4) Takeda proposes that the DMC informs Takeda of its intentions to conduct an interim analysis prior to 550 MACE. Takeda would in turn contact the Agency and suggest that, without Takeda being involved, direct discussions between the DMC and the Division occur regarding the appropriateness of such an unplanned analysis and potentially stopping the study prior to reaching the protocol defined first interim analysis and its potential impact on (b) (4) Does the Agency agree with this approach? Takeda will gain DMC's agreement with this proposal after it is agreed by the Agency.

In summary, Takeda is no longer planning on submitting a proposal to the Agency for consideration, but would appreciate a response to the questions posed above to ensure that there are no outstanding issues related to the ongoing conduct of EXAMINE prior to the filing of the NDA re-submissions."

FDA response to Takeda's June 28, 2011, email:

We understand you to say that you do not plan to conduct an analysis with respect to the 1.3 margin before the next pre-specified interim analysis at 550 events as was suggested during the teleconference. Therefore the first planned interim analysis for testing the 1.3 non-inferiority margin will occur at 550 events.

(b) (4)

(b) (4)

We agree to direct discussion with the DMC without Takeda involvement regarding the appropriateness of any unplanned analyses that may potentially stop the study prior to reaching the protocol defined first interim analysis at 550 events. (b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Sponsor will submit an updated summary of the data contained in the upcoming NDA resubmissions	Sponsor	Submitted by email on July 8, 2011.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

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/s/

MEHREEN HAI
07/15/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: Follow-up to June 20 tcon
Date: Wednesday, June 22, 2011 4:20:02 PM

Hi Sandy,
I received your voicemail this morning, and I'm sorry I haven't been able to call you back. I'll call you tomorrow, but in the meantime, we had the following comments that we wanted to convey to you as a follow-up to the June 20th tcon:

During the June 20th, 2011 teleconference with the Agency to discuss NDA 022271 and NDA 022426, Takeda discussed the first interim analysis of the EXAMINE trial. The first interim analysis was conducted according to the pre-specified plan after (b) (4) MACE events have been observed in EXAMINE. According to Takeda, the results of this interim analysis achieved the 1.8 non-inferiority margin for the relative risk of MACE. The EXAMINE protocol states that the next interim analysis will test for a non-inferiority margin of 1.3 after 550 events have been observed. Takeda discussed their wish to deviate from the original EXAMINE protocol to allow for an interim analysis for non-inferiority, (b) (4) The timing proposed for this additional interim analysis, in terms of number of events, was not discussed during the teleconference.

In general, data driven changes in the timing of interim analyses present a challenge and are to be avoided. It is often difficult or impossible to evaluate the statistical properties of tests conducted at these data driven interim looks. Both Takeda and the Agency should try to be as objective as possible when writing and reviewing proposed changes to a statistical analysis plan. In the case of the EXAMINE trial, it is known that the non-inferiority margin of 1.8 was met at (b) (4) events. This information sets a bound for the observed relative risk of MACE at (b) (4) events. Therefore all additional, not previously planned, interim analyses in EXAMINE are unblinded to the available data.

During the teleconference, the Agency agreed to further discuss Takeda's proposal. We recommend that you consider that any additional interim analyses in the EXAMINE trial should maintain the Type I error for non-inferiority, and should minimize the potential bias resulting from knowing the results of the first interim analysis. The following two approaches meet these criteria; you may propose other approaches as long as they maintain Type I error and minimize bias:

1) Use of a Peto-type stopping rule. This approach spends a very low alpha

at each interim look and allows for an unspecified number of interim looks. 2) Consider using the first (b) (4) events in the EXAMINE trial as a pilot study from which to estimate the statistical characteristics of the remainder of the study. The results of the additional proposed interim analysis at n events would be based only on the last n (b) (4) events.

We also would like to remind Takeda of our interest, as part of the complete response submission, in a subgroup analysis that evaluates the primary and secondary endpoints of the EXAMINE study, according to subjects with an ACS event <= 2 months versus subjects with an ACS event > 2 months prior to randomization.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
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/s/

MEHREEN HAI
06/22/2011

From: Hai, Mehreen
To: "Cosner, Sandra (TGRD)";
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission
Date: Thursday, May 26, 2011 2:41:31 PM

Hi Sandy,
We are confirmed for the tcon on Monday, June 20, 2011, from 1:00 - 2:00 PM (Eastern).
The attendees will be Dr. Mary Parks, Dr. Ilan Irony, Dr. Hylton Joffe, Dr. Valerie Pratt, Dr. Eugenio Andraca-Carrera and myself. If there are any additions/changes, I will let you know closer to the date of the tcon.

Can you please provide a call-in number?
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
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From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Thursday, May 26, 2011 12:30 PM
To: Hai, Mehreen
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission

Dear Mehreen,
Thank you so much for responding so quickly and accommodating our earlier request. June 20th from 1- 2:00 PM will work for our Takeda team. Can you please confirm if this is Eastern time? Also, will you be providing a call in number and also confirming the attendees from the FDA staff?
Thank you again.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-7870
Email: scosner@tgrd.com

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Thursday, May 26, 2011 10:11 AM
To: Cosner, Sandra (TGRD)
Subject: RE: NDA 22-271 and NDA 22-426 Meeting Request Submission

Hi Sandy,
We did our best to schedule your tcon as soon as possible, but I'm afraid the earliest we were able to schedule for is June 20, 1:00 - 2:00 PM. Does this work for you?

Please let me know.
Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
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From: Cosner, Sandra (TGRD) [mailto:scosner@tgrd.com]
Sent: Wednesday, May 25, 2011 4:15 PM
To: Hai, Mehreen
Subject: NDA 22-271 and NDA 22-426 Meeting Request Submission

Dear Mehreen,
We are submitting a meeting request today for the alogliptin and the alogliptin/pioglitazone FDC NDAs (22-271 and 22-462, respectively). I have included the submission as an attachment for your reference. This is following recent emails in April and May between Takeda and Dr. Parks of our intent to schedule a teleconference with the Agency within the next couple of weeks prior to our resubmissions to the Complete Response letters. We look forward to discussing these few issues with the Agency soon.
Please let me know if you have any questions.
Kind regards,
Sandy

Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs Strategy
Takeda Global Research and Development Center, Inc.
Phone (224) 554-1957
Fax (224) 554-7870
Email: scosner@tgrd.com

###
The information contained in this communication is confidential and may be privileged. It is intended only for the use of the addressee and is the property of Takeda. Unauthorized use, disclosure, or copying of this communication, or any part thereof, is strictly prohibited and may be unlawful. If you received this communication in error, please notify me immediately by return e-mail and destroy this communication and all copies thereof, including all attachments.

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/s/

MEHREEN HAI
05/26/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

GENERAL ADVICE

Takeda Global Research & Development Center, Inc.
Attention: Sandra D. Cosner, R.Ph.
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Cosner:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets and for alogliptin and pioglitazone fixed-dose combination tablets.

We also refer to the minutes that we issued on March 16, 2010, for the End-of-Review meeting that was held on February 23, 2010 between representatives of your firm and the FDA. The purpose of the meeting was to discuss the planned resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426. Finally, we refer to your submission dated April 13, 2010, containing comments and requested revisions to the official meeting minutes.

Please find below our responses to your requested revisions. The text from the original meeting minutes is shown in italic font, your comments are underlined, and our current responses are shown in bold font. Please note that our responses were previously communicated to you by email on May 5, 2010.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- *Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.*
- *In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.*
- *For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).*

Meeting Discussion: The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

TGRD Comment: Regarding bullet #3, TGRD explained that majority of the infections that will occur with alogliptin will be non-serious and therefore, organism types are unlikely to be determined or available. For infections that are serious adverse events, TGRD noted that organism type will not be captured in the clinical database, but if assessed, will be reported in the patient narrative. TGRD recalls during the meeting the Division accepting the reasons that analysis of these data are not possible. Therefore, TGRD would like to suggest the following revision to the third paragraph to capture the meeting discussions more accurately:

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor indicated that for infections that are serious adverse events, if organism type is assessed, it will be reported in the patient narrative. However, no analysis of such data will be performed since organism type will not be captured in the clinical database. The Division agreed with this approach.

FDA Response: We find your revision acceptable.

Question 18: Does the Agency agree with Takeda's proposal (b) (4)

FDA Pre-Meeting Response: No, we do not agree. The proposal (b) (4) *will be a review issue.*

(b) (4)

(b) (4)

[redacted]

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Copy of letter with meeting minutes dated March 16, 2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on February 23, 2010. The purpose of the meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Review Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Review

Meeting Date and Time: February 23, 2010, 1:30 PM – 2:30 PM (Eastern)
Meeting Location: White Oak Campus, Building 22, Silver Spring, MD

Application Number: NDA 022271 and NDA 022426
Product Name: Nesina (alogliptin) Tablets and
(b) (4) (alogliptin/pioglitazone FDC) Tablets
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Takeda Global Research & Development Center, Inc.

Meeting Chair: Valerie Pratt, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II (ODE II)
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D., M.M.Sc.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Linda Galgay, R.N.	Regulatory Project Manager, DMEP
Arlet Nedeltcheva-Peneva, M.D.	Clinical Reviewer, DMEP

SPONSOR ATTENDEES

Thomas Strack, M.D.	Vice President, Clinical Science
Penny Fleck, M.T.	Director, Clinical Science
Neila Smith, M.D.	Senior Medical Director, Pharmacovigilance
Michie Hisada, M.D.	Medical Director, Pharmacovigilance
Craig Wilson, Ph.D.	Principal Statistician, Biostatistics
Vipin Arora, Ph.D.	Associate Director, Biostatistics
Dan Bollinger, R.Ph.	Principal Scientist, Pharmaceutical Science

Rebecca Adams	Assistant Project Director, Project Management
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Sangeeta Gupte, Ph.D.	Manager, Regulatory Affairs
Christie Idemoto, M.S.	Associate Director, Regulatory Affairs
Yukari Nishikata	Senior Director, Takeda Japan Liaison
Riccardo Camisasca, M.D.	Medical Director, Clinical Science (Europe)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 21-073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

The purpose of this meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on February 20, 2010, follow in bold. A summary of the meeting discussion is shown in italicized bold font.

Question 1: Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

FDA Preliminary Response: Yes, but with exceptions noted in the comments below.

Meeting Discussion: There was no discussion.

Question 2: Does the Agency agree with Takeda's plan to summarize all integrated safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently?

Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

Meeting Discussion*: *The sponsor clarified that the question pertains only the location of the integrated safety data.

Study 009 will not be included in the integrated safety analysis for the fixed-dose combination (FDC) product because these subjects were on a thiazolidinedione (TZD) for months to years before starting alogliptin, whereas the subjects in the proposed integrated analysis will be randomized to simultaneously start alogliptin + pioglitazone. Study 009 was not included in the integrated analyses of the original NDAs for the same reason. The Division concurred that it is acceptable to not include Study 009 in the integrated analysis for the FDC product in the Complete Response.

Question 3: For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

FDA Preliminary Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

Meeting Discussion*: *There was no discussion.

Question 4: Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

FDA Preliminary Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

***Meeting Discussion**: The sponsor agreed to bullets #1-2. The sponsor stated that adverse events will be summarized by pooled study population and in the newly completed individual studies. Hyperlinks will be provided to adverse events in the study reports submitted with the original NDAs. The Division stated that this approach is acceptable.*

Question 5: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, these are acceptable.

***Meeting Discussion**: There was no discussion.*

Question 6: Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

***Meeting Discussion**: The sponsor clarified that even after the 1.3 goalpost is met, the study will continue until a minimum of 550 events are captured; this should result in a median study duration of 2 years. The Division stated that this is acceptable.*

The sponsor sought confirmation that the proposed sequence of hypothesis testing is acceptable (specifically, testing the hazard ratio of the secondary MACE [H03] prior to the primary MACE [H04]). The sponsor stated that this approach was chosen because there will be more events in the secondary MACE endpoint, (b) (4) (b) (4)

The Division stated that the additional table shell emailed in February pertaining to data presentation for the MACE endpoints is acceptable and sought clarification of which cardiovascular events will be sent for adjudication. The sponsor stated that relevant preferred terms are identified based on an algorithm, investigators are then asked to complete a package for these events, and this package is then forwarded to the (b) (4) *for adjudication. The sponsor agreed to submit the selection algorithm to the Division for review. The sponsor confirmed that the NDA will include explanations for those adverse events that are coded as*

myocardial infarction or stroke based on investigator verbatim terms but that are downgraded by the adjudication committee.

Question 7: Should the Agency find the statistical methodology and fixed, pre-specified order acceptable, (b) (4)

FDA Preliminary Response: It is premature at this point to answer Question 7, as labeling will be a review issue.

Meeting Discussion: There was no discussion.

Question 8: A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

FDA Preliminary Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of Study 402 in addition to the required renal safety analysis?

Meeting Discussion: The sponsor clarified that all adverse event data will be submitted. The laboratory data submitted will be consistent with the information presented in the integrated analysis of safety. The Division agreed that this is acceptable.

The Division sought clarification on how data integrity will be maintained once the 1.8 goalpost is met given the meeting package's description of internal blinded and unblinded teams. The sponsor clarified that they have experience in this area (i.e. study OPI-004) and have detailed Standard Operating Procedures that cover splitting the internal team into a blinded and an unblinded team. Unblinded team members will not cross back to the blinded team or vice versa. Firewalls protect the data. Systems can be reviewed to see who accessed data when. The Data Monitoring Committee is an independent committee. The Division agreed that this is acceptable.

Question 9: Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

***Meeting Discussion*: The sponsor clarified that CV safety will be reviewed in study 402 alone and in Study 402 and all other controlled phase 2-3 trials combined. The sponsor does not plan to conduct a MACE analysis of phase 2-3 trials excluding Study 402, as the remaining trials likely have too few events (~30-40) to determine CV safety. Furthermore, the CV events for most of the phase 2-3 trials, excluding the newly completed trials, were reviewed in the previous NDA submission. The Division agreed with the sponsor's proposed approach.**

Question 10: Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

FDA Preliminary Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

***Meeting Discussion*: The sponsor clarified that 335 days refers to the lower bound of the definition of one year (i.e. 365±30 days) based on the window for the 1-year clinic visit. As subjects do not always present themselves for study visits at precisely 1 year (365 days), this definition is used. It is the same definition used in the previous NDA submissions. Furthermore, the sponsor's estimate that there will be controlled data for 500 patients with at least 1-year exposure to alogliptin is based on this definition.**

The Division agreed that this definition is acceptable for meeting the 1-year exposures requested in the Complete Response Letter. However, the Division requested that the sponsor also calculate exposure at ≥365 days. The sponsor agreed.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

***Meeting Discussion*: The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.**

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

Question 12: Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

FDA Preliminary Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

***Meeting Discussion*: There was no discussion.**

Question 13: Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

FDA Preliminary Response: Yes, we agree with your plan to submit patient narratives for the events agreed to in question 12 (b) (4)

***Meeting Discussion*: There was no discussion.**

Question 14: Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

FDA Preliminary Response: Yes, we agree.

Meeting Discussion*: The sponsor sought clarification that the Division agrees with the sponsor's justification and plan to not manufacture alogliptin+pioglitazone FDC tablets using alogliptin 6.25 mg** (b) (4) ***The Division agreed.

The sponsor asked if they need to address this issue further in the NDA resubmission. The Division stated that it is acceptable to refer to the agreement reached in these meeting minutes.

Question 15: Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

FDA Preliminary Response: The analyses and proposed data presentation are acceptable.

Meeting Discussion: There was no discussion.

Question 16: With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

FDA Preliminary Response: The proposed analyses are acceptable.

Meeting Discussion: There was no discussion.

Question 17: In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

FDA Preliminary Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

Meeting Discussion: The sponsor clarified that this analysis will be based on changes between two groups (normal/mild renal impairment vs. moderate/severe renal impairment). This approach is consistent with the randomized strata. The Division agreed to this approach.

Question 18: Does the Agency agree with Takeda's proposal [redacted] (b) (4)

FDA Preliminary Response: No, we do not agree. The proposal [redacted] (b) (4) **will be a review issue.**

(b) (4)

(b) (4)

Meeting Discussion*: *There was no discussion.

Question 20: Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

FDA Preliminary Response: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Meeting Discussion*: *There was no discussion.

Question 21: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

FDA Preliminary Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Meeting Discussion: There was no discussion.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

FDA Preliminary Response: This decision will be made after the resubmission of these NDAs.

Meeting Discussion: There was no discussion.

Question 23: If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and '(b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and '(b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

FDA Preliminary Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Meeting Discussion: The Division explained that re-review of the previously proposed trade names is automatically conducted during the review cycle upon receipt of the NDA resubmission(s).

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

FDA Preliminary Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.

Please also refer to the Guidance for Industry entitled "*Contents of a Complete Submission for the Evaluation of Proprietary Names*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Meeting Discussion: The Division explained that submissions requesting trade name review should be submitted directly to the attention of the Office of Surveillance and Epidemiology. If the sponsor chooses to submit new trade names prior to the resubmission in response to the Complete Response letters, the review will follow the IND review timeline (i.e. 180 days).

Question 25: Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

FDA Preliminary Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)

Meeting Discussion*: The sponsor understood that the Division cannot comment on whether or not the proposed pediatric study will satisfy PREA requirements.** (b) (4) ***The Division stated that our general approach has been to study new antidiabetic therapies both as monotherapy and as add-on to metformin. The Division also stated that it is unlikely that these pediatric studies will yield useful information on beta-cell preservation.

Question 26: Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

FDA Preliminary Response: We cannot enter into an agreement regarding a written request until after NDA approval.

***Meeting Discussion*: There was no discussion.**

Other FDA Comments:

1. When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)

***Meeting Discussion*: The sponsor agreed.**

2. It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.

***Meeting Discussion*: The sponsor agreed.**

Additional discussion: The sponsor currently has 50 subjects enrolled in study 402 in the United States. The sponsor plans to respond to the Complete Response letters to the NDAs in 2012.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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

/s/

MEHREEN HAI
03/16/2010

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

/s/

MEHREEN HAI
09/23/2010

From: Hai, Mehreen
To: "Idemoto, Christie Ann (TGRD)";
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update
Date: Wednesday, May 05, 2010 1:59:50 PM

Hi again Christie,
Regarding your suggested revisions to the FDA meeting minutes for the End-of-Review meeting for NDA 22-271 (alogliptin) and NDA 22-426 (alogliptin-pioglitazone FDC), that you submitted on April 13, 2010, we accept your suggested revisions, and will update our meeting minutes accordingly.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Tuesday, May 04, 2010 6:13 PM
To: Hai, Mehreen
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update

Thank you, Mehreen.

Christie Ann Idemoto
☎ Office: 847.582.3506 Cell: (b) (6)

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Tuesday, May 04, 2010 1:08 PM
To: Idemoto, Christie Ann (TGRD)
Subject: RE: IND 69,707/NDA 22-271 Alogliptin - Status Update

Hi Christie,
Will get back to you within a day or so with responses to both.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Monday, May 03, 2010 1:30 PM
To: Hai, Mehreen
Subject: IND 69,707/NDA 22-271 Alogliptin - Status Update

Hi Mehreen,

Hope all is well.
I am writing to follow-up on a few pending items. Do you have an estimated timeframe as to when TGRD can expect a response from the Division regarding the following?

1. TGRD's request to use of a different MDRD formulation for patients enrolled in sites in Japan (see email trail below)
2. TGRD's comments/suggested revisions to official minutes from Feb 23 Type B meeting (refer to amendment to NDA 22-271 and NDA 22-426, dated April 13, 2010)

Please let me know if you have any questions.

Thanks very much,

Christie

Christie Ann Idemoto
☎ Office: 847.582.3506 Cell: (b) (6)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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/s/

MEHREEN HAI
05/05/2010

From: Hai, Mehreen
To: "Idemoto, Christie Ann (TGRD)";
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission
Date: Tuesday, April 20, 2010 2:39:47 PM

Hi Christie,
We have finished reviewing the lists of PT terms that were submitted on March 15, 2010, and have found them acceptable. Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Tuesday, April 13, 2010 5:42 PM
To: Hai, Mehreen
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Mehreen,

I apologize for the confusion. Let me try to clarify – there are two reasons new terms have been added to the skin reaction PT list:

1. New terms added as a result of versioning from MedDRA 10.0 (version used for the original NDA) to MedDRA 12.1
   - These terms are highlighted in yellow and listed as NEW in the attached.

2. New terms added as result of the Division's recommendation to include terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue
   - These terms are listed as NEW (but not highlighted in yellow) in the attached.

If you still need further clarification or have additional questions, please contact me directly. I am happy to discuss by phone.

Thanks,
Christie

_____
Christie Ann Idemoto
(Office: 847.582.3506 Cell: (b) (6)

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Tuesday, April 13, 2010 10:41 AM
To: Idemoto, Christie Ann (TGRD)
Subject: RE: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Christie,
We should be able to review the PT terms in another week or so. But we are a little bit confused about which of the PT terms are recently added, that we need to particularly focus on. Can you please clarify that?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073

Fax: 301-796-9712

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Friday, April 09, 2010 11:34 AM
To: Hai, Mehreen
Subject: FW: alogliptin NDA 22-271: follow-up on March 15 submission

Hi Mehreen,

Do you have a status update on the Division's review of the attached lists of PT terms?

Any questions, please let me know.

Thanks,
Christie

_____
Christie Ann Idemoto
(Office: 847.582.3506 Cell: (b) (6)

From: Idemoto, Christie Ann (TGRD)
Sent: Wednesday, March 24, 2010 2:32 PM
To: Hai, Mehreen
Subject: alogliptin NDA 22-271: follow-up on March 15 submission

Dear Mehreen,

Thank you very much for sending Takeda the FDA's meeting minutes from our February 23 Type B meeting. We are currently reviewing the minutes in detail and will advise you if we have any significant differences in understanding.

On March 15, 2010, we submitted TGRD's Type B meeting minutes to NDA 22-271; and, in addition (based on action items from the Type B meeting), the following were also provided for FDA's review and comment:

- List of MedDRA PT Terms for PCDR analysis
- List of MedDRA PT Terms for CEC adjudication

Please let me know when we can expect FDA to complete their review of the above PT lists. I have attached these PT lists + submission cover letter to this email for ease of review.

Any questions, please let me know.

Thanks very much in advance,

Christie

_____
Christie Ann Idemoto
Associate Director, Regulatory Affairs
Takeda Global Research & Development Center, Inc.
+ 675 N. Field Drive, Lake Forest, IL 60045
(Office: 847.582.3506
Cell: (b) (6)
* Email: cidemoto@tgrd.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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/s/

MEHREEN HAI
04/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on February 23, 2010. The purpose of the meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Review Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Review

Meeting Date and Time: February 23, 2010, 1:30 PM – 2:30 PM (Eastern)
Meeting Location: White Oak Campus, Building 22, Silver Spring, MD

Application Number: NDA 022271 and NDA 022426
Product Name: Nesina (alogliptin) Tablets and
(b) (4) (alogliptin/pioglitazone FDC) Tablets
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Takeda Global Research & Development Center, Inc.

Meeting Chair: Valerie Pratt, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II (ODE II)
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D., M.M.Sc.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Linda Galgay, R.N.	Regulatory Project Manager, DMEP
Arlet Nedeltcheva-Peneva, M.D.	Clinical Reviewer, DMEP

SPONSOR ATTENDEES

Thomas Strack, M.D.	Vice President, Clinical Science
Penny Fleck, M.T.	Director, Clinical Science
Neila Smith, M.D.	Senior Medical Director, Pharmacovigilance
Michie Hisada, M.D.	Medical Director, Pharmacovigilance
Craig Wilson, Ph.D.	Principal Statistician, Biostatistics
Vipin Arora, Ph.D.	Associate Director, Biostatistics
Dan Bollinger, R.Ph.	Principal Scientist, Pharmaceutical Science

Rebecca Adams	Assistant Project Director, Project Management
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Sangeeta Gupte, Ph.D.	Manager, Regulatory Affairs
Christie Idemoto, M.S.	Associate Director, Regulatory Affairs
Yukari Nishikata	Senior Director, Takeda Japan Liaison
Riccardo Camisasca, M.D.	Medical Director, Clinical Science (Europe)

1.0 BACKGROUND

Takeda Global Research & Development Center, Inc. (TGRD) submitted NDA 022271 for alogliptin on December 27, 2007, and NDA 022426 for alogliptin-pioglitazone fixed-dose combination on September 19, 2008. Alogliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist, and was approved by the FDA on July 15, 1999, under NDA 21-073 (Tradename: Actos). Complete response letters were issued on June 26, 2009, for NDA 022271 and on September 2, 2009 for NDA 022426.

The purpose of this meeting was to discuss the resubmissions in response to the Complete Response letters that issued for NDA 022271 and NDA 022426.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the Sponsor on February 20, 2010, follow in bold. A summary of the meeting discussion is shown in italicized bold font.

Question 1: Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

FDA Preliminary Response: Yes, but with exceptions noted in the comments below.

Meeting Discussion: There was no discussion.

Question 2: Does the Agency agree with Takeda's plan to summarize all integrated safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

FDA Preliminary Response: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently?

Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

Meeting Discussion*: *The sponsor clarified that the question pertains only the location of the integrated safety data.

Study 009 will not be included in the integrated safety analysis for the fixed-dose combination (FDC) product because these subjects were on a thiazolidinedione (TZD) for months to years before starting alogliptin, whereas the subjects in the proposed integrated analysis will be randomized to simultaneously start alogliptin + pioglitazone. Study 009 was not included in the integrated analyses of the original NDAs for the same reason. The Division concurred that it is acceptable to not include Study 009 in the integrated analysis for the FDC product in the Complete Response.

Question 3: For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

FDA Preliminary Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

Meeting Discussion*: *There was no discussion.

Question 4: Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

FDA Preliminary Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

Meeting Discussion*: *The sponsor agreed to bullets #1-2. The sponsor stated that adverse events will be summarized by pooled study population and in the newly completed individual studies. Hyperlinks will be provided to adverse events in the study reports submitted with the original NDAs. The Division stated that this approach is acceptable.

Question 5: Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

FDA Preliminary Response: Yes, these are acceptable.

Meeting Discussion*: *There was no discussion.

Question 6: Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

Meeting Discussion*: *The sponsor clarified that even after the 1.3 goalpost is met, the study will continue until a minimum of 550 events are captured; this should result in a median study duration of 2 years. The Division stated that this is acceptable.

The sponsor sought confirmation that the proposed sequence of hypothesis testing is acceptable (specifically, testing the hazard ratio of the secondary MACE [H03] prior to the primary MACE [H04]). The sponsor stated that this approach was chosen because there will be more events in the secondary MACE endpoint, (b) (4)

The Division stated that the additional table shell emailed in February pertaining to data presentation for the MACE endpoints is acceptable and sought clarification of which cardiovascular events will be sent for adjudication. The sponsor stated that relevant preferred terms are identified based on an algorithm, investigators are then asked to complete a package for these events, and this package is then forwarded to the (b) (4) ***for adjudication. The sponsor agreed to submit the selection algorithm to the Division for review. The sponsor confirmed that the NDA will include explanations for those adverse events that are coded as***

myocardial infarction or stroke based on investigator verbatim terms but that are downgraded by the adjudication committee.

Question 7: Should the Agency find the statistical methodology and fixed, pre-specified order acceptable, (b) (4)

FDA Preliminary Response: It is premature at this point to answer Question 7, as labeling will be a review issue.

Meeting Discussion: There was no discussion.

Question 8: A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

FDA Preliminary Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of Study 402 in addition to the required renal safety analysis?

Meeting Discussion: The sponsor clarified that all adverse event data will be submitted. The laboratory data submitted will be consistent with the information presented in the integrated analysis of safety. The Division agreed that this is acceptable.

The Division sought clarification on how data integrity will be maintained once the 1.8 goalpost is met given the meeting package's description of internal blinded and unblinded teams. The sponsor clarified that they have experience in this area (i.e. study OPI-004) and have detailed Standard Operating Procedures that cover splitting the internal team into a blinded and an unblinded team. Unblinded team members will not cross back to the blinded team or vice versa. Firewalls protect the data. Systems can be reviewed to see who accessed data when. The Data Monitoring Committee is an independent committee. The Division agreed that this is acceptable.

Question 9: Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

FDA Preliminary Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

***Meeting Discussion*: The sponsor clarified that CV safety will be reviewed in study 402 alone and in Study 402 and all other controlled phase 2-3 trials combined. The sponsor does not plan to conduct a MACE analysis of phase 2-3 trials excluding Study 402, as the remaining trials likely have too few events (~30-40) to determine CV safety. Furthermore, the CV events for most of the phase 2-3 trials, excluding the newly completed trials, were reviewed in the previous NDA submission. The Division agreed with the sponsor's proposed approach.**

Question 10: Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

FDA Preliminary Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

***Meeting Discussion*: The sponsor clarified that 335 days refers to the lower bound of the definition of one year (i.e. 365±30 days) based on the window for the 1-year clinic visit. As subjects do not always present themselves for study visits at precisely 1 year (365 days), this definition is used. It is the same definition used in the previous NDA submissions. Furthermore, the sponsor's estimate that there will be controlled data for 500 patients with at least 1-year exposure to alogliptin is based on this definition.**

The Division agreed that this definition is acceptable for meeting the 1-year exposures requested in the Complete Response Letter. However, the Division requested that the sponsor also calculate exposure at ≥365 days. The sponsor agreed.

Question 11: Does the Agency agree with Takeda's definitions for the special interest adverse events?

FDA Preliminary Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

***Meeting Discussion*: The sponsor agreed to broaden its definition of PCDR to include skin ulcer-related events (bullet #1) and to submit the new list of preferred terms for review.**

Regarding bullet #2, the sponsor clarified that serum amylase and pancreatitis data are only routinely collected in study 402. These data will be submitted. Laboratory and imaging data in confirmed cases of pancreatitis (including those cases occurring in the other studies) will also be submitted.

Regarding bullet #3, the majority of infections will likely be nonserious events. Thus, only sporadic information on the organism type may be available. The sponsor agreed to analyze all available data. The Division agreed with this approach.

Question 12: Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

FDA Preliminary Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

***Meeting Discussion*: There was no discussion.**

Question 13: Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

FDA Preliminary Response: Yes, we agree with your plan to submit patient narratives for the events agreed to in question 12 (b) (4)

***Meeting Discussion*: There was no discussion.**

Question 14: Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

FDA Preliminary Response: Yes, we agree.

Meeting Discussion*: The sponsor sought clarification that the Division agrees with the sponsor's justification and plan to not manufacture alogliptin+pioglitazone FDC tablets using alogliptin 6.25 mg** (b) (4) ***. The Division agreed.

The sponsor asked if they need to address this issue further in the NDA resubmission. The Division stated that it is acceptable to refer to the agreement reached in these meeting minutes.

Question 15: Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

FDA Preliminary Response: The analyses and proposed data presentation are acceptable.

Meeting Discussion: There was no discussion.

Question 16: With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

FDA Preliminary Response: The proposed analyses are acceptable.

Meeting Discussion: There was no discussion.

Question 17: In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

FDA Preliminary Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

Meeting Discussion: The sponsor clarified that this analysis will be based on changes between two groups (normal/mild renal impairment vs. moderate/severe renal impairment). This approach is consistent with the randomized strata. The Division agreed to this approach.

Question 18: Does the Agency agree with Takeda's proposal [redacted] (b) (4)

FDA Preliminary Response: No, we do not agree. The proposal [redacted] (b) (4) **will be a review issue.**

(b) (4)

(b) (4)

<u>Meeting Discussion</u>: There was no discussion.

<u>Question 20</u>: Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

<u>FDA Preliminary Response</u>: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

<u>Meeting Discussion</u>: There was no discussion.

<u>Question 21</u>: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

FDA Preliminary Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Meeting Discussion: There was no discussion.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

FDA Preliminary Response: This decision will be made after the resubmission of these NDAs.

Meeting Discussion: There was no discussion.

Question 23: If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and '[redacted] (b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and '[redacted] (b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

FDA Preliminary Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Meeting Discussion: The Division explained that re-review of the previously proposed trade names is automatically conducted during the review cycle upon receipt of the NDA resubmission(s).

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

FDA Preliminary Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.

Please also refer to the Guidance for Industry entitled "*Contents of a Complete Submission for the Evaluation of Proprietary Names*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

Meeting Discussion: The Division explained that submissions requesting trade name review should be submitted directly to the attention of the Office of Surveillance and Epidemiology. If the sponsor chooses to submit new trade names prior to the resubmission in response to the Complete Response letters, the review will follow the IND review timeline (i.e. 180 days).

Question 25: Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

FDA Preliminary Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)

Meeting Discussion*: The sponsor understood that the Division cannot comment on whether or not the proposed pediatric study will satisfy PREA requirements.** (b) (4) [redacted] ***The Division stated that our general approach has been to study new antidiabetic therapies both as monotherapy and as add-on to metformin. The Division also stated that it is unlikely that these pediatric studies will yield useful information on beta-cell preservation.

Question 26: Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

FDA Preliminary Response: We cannot enter into an agreement regarding a written request until after NDA approval.

***Meeting Discussion*: There was no discussion.**

Other FDA Comments:

1. When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)

***Meeting Discussion*: The sponsor agreed.**

2. It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.

***Meeting Discussion*: The sponsor agreed.**

Additional discussion: The sponsor currently has 50 subjects enrolled in study 402 in the United States. The sponsor plans to respond to the Complete Response letters to the NDAs in 2012.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

No action items.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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

/s/

MEHREEN HAI
03/16/2010

Medical Officer Review
Division of Metabolism and Endocrinology Products

NDAs 22-271 & 22-426
Name of drugs: Alogliptin & alogliptin/pioglitazone FDC
Sponsor: Takeda
Relevant INDs: 69,707 & 73,193
Indication: Type 2 diabetes mellitus (T2DM)

Type of Meeting: Type B, End of Review (EOR)
Date of Submission: January 21, 2010
Date of Meeting: February 23, 2010

Medical Reviewer: Valerie Pratt, M.D.
Medical Team Leader: Hylton Joffe, M.D.

Background: The sponsor submitted NDAs 22-271 and 22-426 for alogliptin and alogliptin/poiglitazone (A/P) FDC, respectively, for the treatment of T2DM. On June 26 and September 2, 2009, respectively, the applications received a complete response for the following clinical reasons:

- A numerical imbalance in serious cardiovascular (CV) adverse events (AEs), not favoring alogliptin therapy
- The lack of controlled data beyond week 26
- A 70% increase in the mean area under the time-alogliptin concentration (AUC) curve in subjects with mild renal impairment compared to subjects with normal renal function in study SYR-322-006
- In NDA 22-426, greater incidences of elevation in BUN, serum creatinine, and urinary albumin/creatinine ratios and greater shifts to mild or moderate renal impairment

The purpose of this EOR meeting is to obtain agreement on the following:

- Content of each NDA resubmission
- CV analyses of
    - CV outcomes study, SYR-322_402 (402)
    - A pooled study of all controlled phase 2 and 3 studies
- Safety updates for alogliptin and A/P FDC tablets

Notes:

- The sponsor is in the process of amending CV protocol 402 and the case report form based on our January 4, 2010 comments. Comments that affect the statistical analysis plan (SAP) for study 402 or safety updates are not reflected in this submission, although applicable changes will be made prior to finalizing the SAPs.

- In February 2010, the sponsor emailed an additional draft table shell (153342_13Jan2010 for study 402) and rationale to be reviewed in conjunction with question 6. They are reviewed below.

Meeting Package Summary: The sponsor plans to resubmit the alogliptin and A/P NDAs in parallel. Since the submission of the original NDAs, 4 controlled clinical studies (3 of which are 52 weeks or longer in duration) have been completed or initiated and 1 open label extension study remains ongoing.

- SYR-322_301: Ongoing, randomized, double blind, placebo controlled, 16 week study evaluating alogliptin and alogliptin coadministered with pioglitazone versus placebo on postprandial lipids in subjects with T2DM. A total of 71 subjects were randomized to either alogliptin 25 mg daily, coadministration of alogliptin 25 mg and pioglitazone 30 mg daily, or placebo. This study should be completed this year. Data from this study will be included in the alogliptin and A/P NDA resubmissions.
- SYR-322_303: Ongoing, randomized, double blind, active controlled, 52 week study evaluating alogliptin versus glipizide in elderly subjects (65-90 years) with T2DM. A total of 441 subjects were randomized to receive 25 mg alogliptin daily or 5 mg glipizide daily (titrated for inadequate control to 10 mg daily). This study should be completed this year. Data from this study will be included in the alogliptin NDA resubmission.
- 01-06-TL-322OPI-004: Recently completed, phase 3, double blind, 52 week study that evaluated the addition of alogliptin versus the titration of pioglitazone in T2DM subjects receiving metformin/pioglitazone combination therapy. A total of 404 subjects received alogliptin 25 mg in addition to pioglitazone 30 mg and metformin ≥1500 mg or maximum tolerated dose (MTD) and 399 subjects received pioglitazone 45 mg and metformin ≥1500 mg or MTD. Data from this study will be included in the alogliptin and A/P NDA resubmissions.
- SYR-322_402 (402): Long term CV outcomes study that was recently initiated to satisfy the requirements of the CV guidance. This is a randomized, double blind, placebo controlled study evaluating the incidence of major adverse CV events (MACE) following treatment with alogliptin compared with placebo in subjects with T2DM and acute coronary syndrome. Approximately 2700 subjects will receive alogliptin (6.25, 12.5 or 25 mg QD based on renal function) and 2700 subjects will receive placebo, in addition to standard of care. The overall duration of this study is dependent on reaching the predefined number of MACE vents, although the maximum length of follow up is expected to be approximately 4.75 years. The median length of study participation for each subject is estimated to be 2 years. A maximum of 4 interim analyses will be conducted in sequential order after approximately 80, 100, 125, and 150 adjudicated events within the primary MACE composite have occurred. Interim data from this study will be included to support the safety of alogliptin.
- SYR-322-OLE-012: Ongoing, 4 year, open label extension study. Interim data from this study was included in the original NDA and 120-day safety update for alogliptin. This study will not be completed at the time of the resubmission, however, serious adverse event (SAE) summary tables and corresponding

narratives for deaths and SAEs for all subjects who had a serious adverse event since the time of the 120-day safety update will be provided in the alogliptin NDA resubmission.

At the time of resubmission, the sponsor proposes that the safety and efficacy of alogliptin and A/P will be supported by 12 phase 2 and 3 controlled studies (including the 4 described above). The clinical overview and summary sections of the NDA resubmission will be updated with results from these new clinical studies. A safety update will summarize safety results from the 4 new studies (301, 303, 402, OPI-004) combined with the phase 2 and 3 controlled studies previously included in the integrated analysis of safety (IAS) (003, 007, 008, 009, 010, and 011), OPI-001, and -002. Data from phase 1 and the ongoing open-label extension study will not be included.

Please refer to Appendices 2 and 3 for the proposed structure of the alogliptin and A/P NDA resubmissions.

Safety Analyses: In the alogliptin NDA resubmission integrated analysis of safety (IAS), study treatment groups will be described as placebo, active comparator, alogliptin 12.5 mg, and alogliptin 25 mg, as well as all alogliptin (6.25, 12.5, 25, 50, and 100 g) and all comparators (i.e. placebo and active). Analyses will be similar to those in the original filing with the following exceptions:

- Cumulative exposure will be summarized for the phase 2 and 3 controlled studies overall and by study
    - *Internal comment: You should summarize exposure for subjects with mild, moderate, and, severe renal impairment.*
    - According to our meeting minutes of the April 27, 2009 Type A meeting, the sponsor estimated that 400-500 patients with moderate renal impairment will have 1 year of exposure to study medication and 80-100 patients with severe renal impairment will have 1 year of exposure to study medication. These numbers represent all exposure, not just alogliptin-exposed patients. We later requested that at least 100 subjects with severe renal impairment have at least 1 year of exposure to alogliptin. However, according to the meeting package, the sponsor anticipates that 400-500 subjects with moderate renal impairment and 80-100 subjects with severe renal impairment will be enrolled in study 402 and exposed for at least 1 year. In the event that this study does not evaluate a sufficient number of subjects with severe renal impairment to satisfy our request, the sponsor plans to conduct a supplementary postmarketing safety study in subjects with severe renal impairment.
        - *Internal comment: According to the April 27, 2009 meeting minutes which were finalized on August 26, 2009, the sponsor stated that at the time of the intermediate analysis that satisfies 1.8, there will not be 1 year of exposure data for all renal impairment patients. However, when study 402 is completed, the sponsor estimated that 200-250 subjects with moderate renal impairment should be exposed to alogliptin for 1 year and at least*

100 subjects with severe renal impairment should be exposed to alogliptin for at least 1 year. The sponsor now states that there may not be 1-year data for 100 patients with severe renal impairment from the pre-approval studies and is proposing a supplemental postmarketing study, if needed (see Question 18 and the associated discussion in the meeting minutes).

- Summary tables will be generated for medical history and concurrent conditions, including subsets of CV history, conditions, and medications
- AEs of special interest: potential cutaneous drug reactions (PCDR, previously used definition), angioedema standardized MedDRA Query (SMQ), acute pancreatitis SMQ, and malignancies SMQ. (The CV-related AE cluster will be replaced by the MACE analyses.)
    - *Internal comment: Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with some other DDP4 inhibitors. However, it was not seen in alogliptin studies in mice, rats, dogs, or monkeys. No remarkable skin lesions or skin-related toxicity were noted in rodent studies. Four- and 13-week monkey studies were designed specifically to examine the potential for drug induced skin lesions. There was no evidence of drug-related skin lesions in clinical observations, macroscopic analyses at necropsy, or histological analyses at necropsy in either monkey study. The NOAEL from skin-related toxicity in the 13 week monkey study was 30 mg/kg/d, which provided approximately 31x expected human exposure. The lack of cutaneous toxicity may be due to alogliptin's high selectivity for DPP4, as opposed to DPP8 and/or DPP9.*

      Your definition of PCDR events includes high level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should include this PCDR events as AEs of special interest and broaden its search criteria to include terms related to ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue.
    - *Internal comment: In addition to describing events of acute pancreatitis as AEs of special interest, please also provide data on serum amylase and lipase and imaging results obtained in patients with suspected or confirmed pancreatitis.*
- Serious special interest AEs and special interest AEs leading to discontinuation will be summarized in addition to the summaries of treatment-emergent adverse events by groupings that were included in the original filing.
- AEs will also be summarized by Baseline and Endpoint renal status.
- In the original submission, the long-term safety of alogliptin was based on 12-month data from the open-label extension study (SYR-322_OLE-012). For the resubmission, long-term safety will be based on 3 controlled studies (303, 402,

and OPI-004), which will provide controlled exposure for 12 months and up to 18 months for some subjects.

- With regard to laboratory evaluations, serum creatinine and estimated glomerular filtration rate (eGFR) estimated by the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations will be summarized in an additional table to evaluate renal function. In addition, shift tables will be used to summarize the number of subjects with normal renal function and mild, moderate, and severe renal impairment at baseline and their corresponding renal function at each post-baseline visit and at endpoint for both the Cockcroft-Gault and MDRD equations. Also, 2 changes will be made to the markedly abnormal criteria for laboratory values. The markedly abnormal criterion for serum creatinine will change from >1.5 x Baseline to >1.5 x Baseline AND >upper limit of normal (ULN) and a criterion will be added to evaluate alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 x ULN in conjunction with total bilirubin >2.0 mg/dL.
    - *Internal comment: You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline). If you wish to also analyze renal data with the revised definition, you may.*

In addition, both the alogliptin and A/P NDA resubmissions will evaluate the following AEs of special interest:

- Infections and infestations (SOC)
- Hepatotoxicity will be evaluated based on DILI Guidance and will include changes from Baseline to Endpoint, incidences of markedly abnormal results, and shift analyses for total bilirubin, AST, ALT, and gamma glutamyl transferase (GGT).
- Renal safety will be evaluated based on changes from baseline to endpoint, incidences of markedly abnormal results, and shift analyses for serum creatinine and eGFR using the Cockcroft-Gault and MDRD equations and the incidence of renal dialysis and kidney transplant.

In the A/P NDA resubmission, the safety update will include data from 4 phase 3 controlled trials (OPI-001, -002, -004, and study 301) that will be pooled into an integrated safety database ("phase 3 controlled studies"). Study groups will be the following: alogliptin, pioglitazone, and A+P. In some tables, data will also be summarized by alogliptin dose.

Internal comment: The sponsor should clarify why it is not including study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the A/P FDC NDA.

The planned analyses are similar to that conducted for the original filing with exceptions as follows: (Please also see comments above, as most also apply to the A/P NDA resubmission.)

- Cumulative exposure will be summarized for the phase 3 controlled studies overall and by study.
- Prior and concomitant CV medications will be summarized as subsets of the overall displays of prior and concomitant medications. CV medical histories and concurrent CV conditions will be summarized as subsets of the overall displays of medical histories and concurrent conditions.
- The adverse event "clusters" presented in the original filing will be replaced with the following groupings of special interest adverse events:
    - PCDR (defined as in the original filing).
    - Angioedema SMQ.
    - Acute pancreatitis SMQ.
    - Malignancies SMQ (narrow scope terms only).
    - Cardiac failure SMQ.
    - Edema (defined as in the original filing).
    - Weight gain (defined as in the original filing).
    - Bone fracture (defined as in the original filing).
- Serious special interest AEs and special interest AEs leading to discontinuation will be summarized in addition to the summaries of treatment-emergent adverse events by groupings that were included in the original filing.
- With regard to laboratory evaluations, serum creatinine and eGFR estimated by the Cockcroft-Gault and MDRD equations will be summarized in an additional table to evaluate renal function. In addition, shift tables will be used to summarize the number of subjects with normal renal function and mild, moderate, and severe renal impairment at baseline and their corresponding renal function at each post-baseline visit and at endpoint for both the Cockcroft-Gault and MDRD equations. Also, 2 changes will be made to the markedly abnormal criteria for laboratory values. The markedly abnormal criterion for serum creatinine will changed from >1.5 x Baseline to (b) (4) and a criterion will be added to evaluate AST >3x ULN in conjunction with total bilirubin >2 mg/dl.

Narratives: The alogliptin NDA resubmission will include patient narratives for events that occurred during studies 101, 103, 301, 303, and 402 and the alogliptin/pioglitazone FDC NDA resubmission will include patient narratives for events that occurred during study OPI-004. Narratives for deaths and other serious adverse events that occurred in the ongoing open-label extension study (012) since the alogliptin 120-day update will be included in module 5 of the alogliptin resubmission. The following narratives will be provided and presented in a similar format as in the original NDA submissions:

- Required Narratives (will be included in the clinical study reports):
    - Deaths.
    - Other serious adverse events.
    - Adverse events that led to study drug discontinuation.
- Others Narratives Previously Requested by FDA (will be included in module 5):
    - ALT/AST laboratory values >3x ULN.
    - Creatine phosphokinase (CPK) laboratory values >5x ULN (CPK was measured only in Study SYR-322_402).
    - Adverse events of pancreatitis.

With regard to other special interest adverse events (i.e. infections, skin reactions, angioedema, malignancy, and renal safety), the sponsor plans to only provide narratives for those subjects who have serious adverse events as limited information will be available for non-serious events. These will be included as part of the SAE narratives in the individual study.

Internal comment: Please provide links to the narratives in the study reports from summary tables and line listings.

For each of the new controlled studies supporting the NDA resubmissions (i.e. 101, 103, 301, 303, 402, and OPI-004), patient narratives will be provided for the events that are agreed upon in Question 11. (b) (4) however, for each of the completed studies (101, 103, 301, 303, and OPI-004), the patient narratives will be accompanied by the respective patient eCRF.

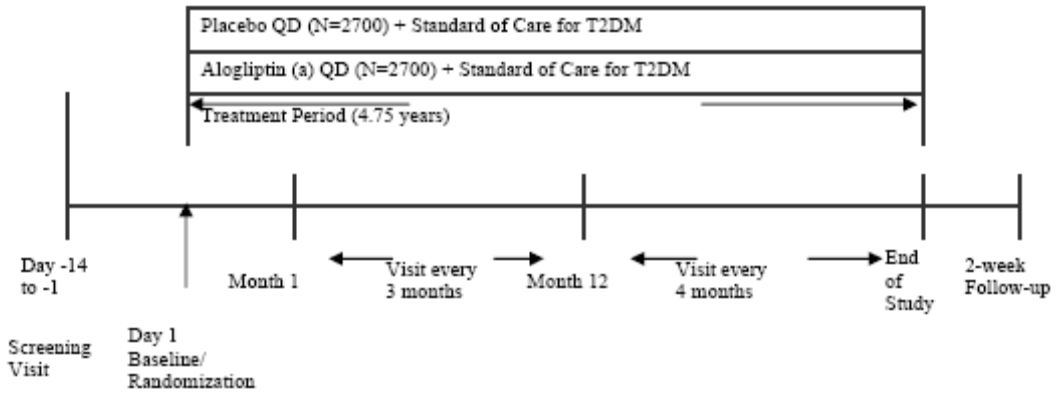
Long-term Safety: The long-term safety of alogliptin will be supported by an integrated analysis of subjects with at least 1-year (defined as 335 days) of exposure to alogliptin from 3 controlled, clinical studies. This analysis will include data from Studies 303, OPI-004, and 402 and will evaluate all adverse events and serious adverse events that occurred in this population as well as adverse events and serious adverse events that occurred in this population with an onset time greater than or equal to 1 year. At the time of the resubmission, controlled data for at least 500 subjects exposed to alogliptin for a minimum of 1 year will be included in this analysis.

Note: The complete response letter for the alogliptin NDA required the sponsor provide controlled data for at least 500 subjects with at least 1 year total exposure to alogliptin.

Internal comment: In your long-term safety analysis, you define 1 year exposure to alogliptin as 335 days. Please also include the number of patients exposed to ≥365 days (a standard year).

Cardiovascular Safety: Study 402 was designed to evaluate MACE. Deaths and adverse events that are potentially MACE in this study will be adjudicated by an independent Cardiovascular Endpoints Committee (CEC) to determine which events to include as MACE in analyses.

Study 402. Study design (Reproduced from the sponsor)



(a) At randomization, subjects will be assigned 25 mg, 12.5 mg, or 6.25 mg QD depending on renal function. Following randomization, dose adjustments will be allowed on the basis of changes in renal function.

Results for the primary endpoint at the time of the interim analysis for assessing non-inferiority will be summarized in the alogliptin resubmission. The primary endpoint is the primary MACE composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. The secondary endpoint is the secondary MACE composite of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization due to unstable angina. The statistical tests for the primary and secondary MACE composite will be conducted in a fixed, pre-specified ordering for the following 4 null hypotheses:

- H01: The hazard ratio of the primary MACE composite is ≥1.8 following treatment with alogliptin compared with placebo.
- H02: The hazard ratio of the primary MACE composite is ≥1.3 following treatment with alogliptin compared with placebo.
- H03: The hazard ratio of the secondary MACE composite is ≥1.0 following treatment with alogliptin compared with placebo.
- H04: The hazard ratio of the primary MACE composite is ≥1.0 following treatment with alogliptin compared with placebo.

Each of the 4 null hypotheses will be tested at the 1-sided 2.5% false-rejection rate. Each hypothesis is tested only if all previously tested hypotheses have been rejected. As a result, the principle of closed testing implies that the overall 1-sided false-rejection rate of the study is maintained at 2.5%.

The primary and secondary endpoint will be analyzed using Cox proportional hazards (CPH) models of the respective composites with treatment as the single factor, stratified by screening renal function (normal renal function/mild renal impairment vs. moderate/severe renal impairment including ESRD) and country.

Null hypotheses H01 and H02 will be tested using group sequential methods and separate O'Brien-Fleming spending functions. Testing for each hypothesis will be conducted using a sequence of upper bounds of 1-sided repeated confidence intervals (CIs) for the true hazard ratio (alogliptin to placebo) derived from the CPH models with critical values chosen to maintain overall simultaneous coverage probabilities of 97.5%.

Null hypotheses H03 and H04 will be tested using conventional (not repeated) 1-sided 97.5% CIs for the true hazard ratio (alogliptin to placebo) derived from CPH models for the primary and secondary endpoints fit at the time H02 is rejected. Statistical superiority of alogliptin to placebo for the respective endpoint will be claimed if a null hypothesis is rejected.

One listing of all investigator-reported CV events identified by a search of CV preferred terms will be provided. The listing will denote the following:

- Investigator-reported CV events that were adjudicated by the CEC to be MACE.
- Investigator-reported CV events that were judged not to be MACE by the CEC.

Note: This approach differs from the July 22 guidance which recommends 3 listings as follows:
1. All investigator-reported CV events that were also adjudicated by the CEC to be events
2. All investigator-reported CV events that were not thought to be events by the CEC
3. All CEC-adjudicated CV events that were not considered to be events by the investigator
As discussed at the January 14, 2010 teleconference, an investigator-endpoint report form will not be used during this study because investigators will not be responsible for assessing whether an event meets a specific endpoint; this will be the role of the CEC only.

Internal comment: At the meeting, we will ask the sponsor to clarify which events are sent to the CEC committee. For relevant events (e.g. events reported by the investigator as MI or stroke) that are not coded as MI or stroke by the CEC, the sponsor should submit an explanation for those AEs.

Note: At the April 27, 2009 meeting, the Sponsor stated that 10-20% of the patients (~300) will be on background pioglitazone therapy at the time of randomization and that approximately 80% of the patients would be on background metformin therapy at the time of randomization.

In the IAS, deaths and AEs that were potentially MACE in the completed studies within the phase 2 and 3 controlled studies group in the IAS will be retrospectively adjudicated by the same CEC and using the same definitions used for Study 402. Events in all 12 studies in the phase 2 and controlled studies group that are deemed to meet the criteria specified for the primary MACE composite in the Study 402 protocol will be analyzed in the IAS.

The number and percentage of subjects with at least 1 MACE will be reported by treatment grouping, including the "All Alogliptin" and "All Comparators" groupings. The first MACE for each subject will also be further summarized by type (CV death, nonfatal MI, and nonfatal stroke). The hazard ratio comparing the All Alogliptin grouping to the All Comparators grouping will be obtained from a CPH model of the time from randomization to the first occurrence of MACE, stratified by study. Subjects without an

event will be censored at the date of their last visit. A 1-sided 97.5% CI for the hazard ratio (alogliptin to placebo) will be reported. A listing of all MACE will be provided.

Internal comments:

- *Please confirm that you will discuss early termination of study 402 with the agency prior to terminating it.*
- *When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) in addition to the required renal safety analysis?*
- *At the meeting we will ask the sponsor to clarify how it will protect the integrity of ongoing study 402 when unblinding data for sequential analyses.*

Renal Dosing and Safety: In the complete response letter for the A/P NDA, the agency raised concern regarding the available dose strengths of the A/P FDC tablet for patients with renal impairment. For patients with moderate renal insufficiency, one-half of the therapeutic dose of alogliptin should be administered. Doses of alogliptin/pioglitazone FDC 12.5 mg/15 mg, 12.5 mg/30 mg and 12.5 mg/45 mg will be available for these patients.

For patients with severe renal insufficiency or ESRD requiring dialysis, alogliptin at one-quarter of the therapeutic dose (6.25 mg daily) and pioglitazone at a therapeutic dose (15, 30, or 45 mg QD) can be coadministered as 2 separate tablets.

(b) (4)

The sponsor believes that patients receiving the A/P FDC who progress to severe renal impairment can appropriately be treated with the coadministration of alogliptin 6.25 mg and pioglitazone. Therefore, the sponsor does not plan to manufacture A/P FDC dose strengths containing 6.25 mg of alogliptin.

The sponsor plans to analyze the safety data from subjects with renal impairment according to the recommendations provided on July 15, 2009. All renal function, efficacy, and safety data will be presented using the MDRD equation and the Cockroft-Gault formula.

At the time of the resubmission, renal safety will be evaluated in Study 402 and in the alogliptin IAS and will be based on the incidence of adverse events by baseline and endpoint renal impairment status and changes from baseline to endpoint, incidences of markedly abnormal results, and shift analyses for serum creatinine and eGFR.

Per the Agency's recommendations, the following criteria will be used for markedly abnormal serum creatinine and eGFR. Note that an additional criterion was added for serum creatinine.

- Serum creatinine:

  - >0.3 mg/dL increase above baseline.
  - ≥2x increase above baseline.
  - >2.0 mg/dL
- eGFR:
  - >25% reduction from baseline.
  - >50% reduction from baseline.

The final analysis for Study 402 will include the analyses described above in addition to the incidence of renal dialysis and kidney transplant and the change from baseline in renal biomarkers, kidney injury molecule-1 (Kim-1) and neutrophil gelatinase-associated lipocalin (NGAL).

Foreign Studies: In addition, safety data from several non-IND studies completed in Japan will be included in the alogliptin NDA resubmission (total subjects 1258). Specifically, 5 controlled phase 2/3 studies, 4 phase 2/3 open-label extension studies, and 3 open-label phase 2 PK studies evaluating alogliptin, and 2 phase 1 studies evaluating A/P have been completed see appendix 1). The 5 controlled studies included 4 12-week studies (CCT-001, 004, 005, and 006) and 1 24-week study (CCT-003). The sponsor will include data on an individual study basis and significant findings with regard to AEs, SAEs, and AEs leading to study drug discontinuation in the alogliptin NDA resubmission.

Phase 1 and Nonclinical Studies: In addition, the following phase 1 studies were completed and will be included in the alogliptin NDA resubmission:

- SYR-322_101: Compared PK of alogliptin 12.5 gm twice daily with 25 mg daily in 28 healthy adults
- SYR-322_103: Evaluated the absolute bioavailability of alogliptin after 12.5 mg intravenous dose and 25 mg oral dose in 21 healthy adults

The sponsor has also completed an alogliptin and metformin range-finding study in rats and has plans to conduct a definitive embryo-fetal study as well.

Data Format: For both resubmissions, the sponsor will provide SAS Version 5 transport files for all clinical data for studies not previously submitted (i.e. 101, 103, 301, 303, OPI-004, and 402 and foreign studies) and the IAS. Data set format and structure will be identical to those previously submitted. The SAS Version 5 transport files will not have a maximum file size limit. Each data set will be accompanied by a data definition table (define.pdf), which will include metadata information, such as variable name, a description of the variable, the type of the variable (numeric, character, date, time) and codes (and decodes). The data definition table will also include a comments field that will provide the method for calculating the derived variables, and the location of raw variables on the respective annotated case report form.

Pediatric Studies: (b) (4)

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(b) (4)

The Sponsor's Questions and the Division's Reponses (in bold):

1. Does the Agency agree with the proposed structure and contents of both NDA resubmissions?

Response: Yes, but with exceptions noted in the comments below.

2. Does the Agency agree with Takeda's plan to summarize all integrated safety data within Module 2.7.4 of both NDA resubmissions and therefore not submit a separate summary report of the integrated analyses within Module 5.3.5.3?

Response: Please clarify. Does the question only pertain to the location of the integrated safety data or are you proposing to present these data differently? Clarify why you are not including Study 009 (alogliptin as add-on combination therapy to pioglitazone) in the integrated safety analysis for the alogliptin/pioglitazone fixed-dose combination NDA.

3. For the Safety Updates, Takeda plans to summarize relevant safety data (adverse events, SAEs, and adverse events leading to discontinuation) from the individual Japanese studies within Module 2.7.4 and provide the final clinical study reports for these non-IND studies in Module 5. Does the Agency find this approach acceptable?

Response: Yes, this is acceptable. Please cite the table numbers in the original study reports and provide hyperlinks where possible.

4. Does the Agency agree that the proposed integrated analyses of the phase 2 and 3 controlled studies as described in the SAPs, and the table shells are adequately designed to address the Agency's requests in Complete Response letters for the both alogliptin alogliptin/pioglitazone safety updates?

Response: Yes, but with the following caveats:

- **Please also summarize duration of exposure to study medication according to baseline renal function (mild, moderate, and, severe renal impairment as calculated by both the Cockcroft-Gault and MDRD formulae).**
- **You define markedly abnormal serum creatinine as >1.5x baseline and >ULN. However, in the previous NDA submission, it was defined as >1.5x baseline. Please analyze renal data using the definition used in the original NDA (i.e. >1.5x baseline) because such an increase in serum creatinine even within the reference range may reflect an important decline in renal function. If you wish to also analyze renal data with the revised definition, you may do so.**
- **Please clarify if adverse events will be summarized in the pooled study population and by individual study (including recently completed studies).**

5. Does the Agency agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

Response: Yes, these are acceptable.

6. Does the Agency agree that the proposed primary and secondary MACE analyses as described in the SAP and the table shells for Study 402 are adequately designed to support the CV safety of alogliptin?

Note from internal meeting: We had a question about how likely it is that Study 402 would be stopped at one of the early interim looks because the 1.3 goal post was met. This refers to the first 4 interim looks after 80, 100, 125 and 150 events when the study is powered to evaluate the 1.8 goal post. Dr. Janice Derr of Statistics believes that this is

very unlikely to happen if we believe that the two study arms actually have the same hazard rate for MACE events. In addition, she notes that the final 3 interim looks to evaluate the 1.3 goal post take place after 550, 600 and 650 events. This design, with the 7 proposed interim looks, has approximately 91% power to evaluate the hazard ratio against the goal post of 1.3.

A concern that underlies this question is the number of patients who will be exposed to alogliptin in Study 402 in the event that it is stopped early. Dr. Derr believes it is the intent in this study to treat all randomized patients for at least one year. She interprets this from the study protocol, section 9.2 (Schedule of observations and procedures). Clinical visits are scheduled at months 1, 3, 6, 9, and month 12 and every 4 months until the end of the study. However, it may be useful to clarify this with Takeda.

Internal comment: At the meeting, we will ask the sponsor to clarify which events are sent to the CEC committee. For relevant events (e.g. events reported by the investigator as MI or stroke) not coded as MI or stroke by the CEC, the sponsor should submit an explanation for those AEs.

Responses: Please clarify the minimum duration of treatment exposure for all patients enrolled in Study 402. If you intend to prematurely terminate Study 402 (e.g., if you meet the 1.3 goalpost based on an interim analysis), you should discuss these plans with FDA before implementation to ensure that FDA agrees that there is sufficient overall exposure to study medication.

7. Should the Agency find the statistical methodology and fixed, pre-specified order acceptable, (b) (4)

Response: It would be premature at this point to answer question 7, as labeling will be a review issue.

8. A table of contents of the proposed tables, listings, and figures to be included in the interim analysis for Study 402 is also provided in Appendix C. Does the Agency agree with the proposed data presentations planned for the alogliptin and alogliptin/pioglitazone FDC resubmissions?

Note from internal meeting: There is a concern about the description of the internal blinded team and the internal unblinded team and their duties in the event that the 1.8 goal post is met, which initiates the submission of the NDA, following which Study 402 is continued until the 1.3 goal post is met or the study is terminated (See Appendix C, p. 35/52, the second paragraph of section 9.15.1 "DMC, unblinded team, and confidentiality of interim data and analysis"). Dr. Todd Sahlroot of Statistics will discuss this issue with Bob O'Neill.

Internal comment: At the meeting we will ask the sponsor to clarify how they will protect the integrity of ongoing study 402 when unblinding data for sequential analyses.

Response: When submitting data to the agency from the sequential MACE analyses, do you intend on submitting full safety data (i.e. adverse events and laboratory data) from the interim analysis of study 402 in addition to the required renal safety analysis?

9. Does the Agency agree that the proposed integrated analysis as described in the SAP and the table shells are adequately designed to support the CV safety of alogliptin?

Response: Please clarify whether the integrated analysis of cardiovascular safety from the controlled Phase 2 and Phase 3 studies, as described in Appendix E, excludes the results from Study 402, the dedicated cardiovascular study. However, we note that it is also acceptable to conduct two analyses, one with and one without Study 402.

10. Does the Agency agree that the proposed analyses and table shells are appropriately designed to assess the long-term safety of alogliptin?

Response: For all analyses of duration of exposure (e.g., Table 8.4.2.6), please also present one-year data using a cutoff of 365 days.

11. Does the Agency agree with Takeda's definitions for the special interest adverse events?

Response: No, we do not agree. Please also do the following:

- **Cutaneous toxicity, including ulceration, necrosis, mixed cell inflammation, hemorrhage, edema and granulation tissue, has been observed with other DDP4 inhibitors. Your definition of PCDR events includes high-level group terms in the immune system disorders SOC and skin and subcutaneous disorders SOC from MedDRA. However, the only ulcer term included is "venous ulcer pain." Although alogliptin does not appear to be associated with cutaneous toxicity in humans, you should broaden the PCDR analyses to include preferred terms related to skin ulceration, skin necrosis, skin mixed cell inflammation, skin hemorrhage, edema and skin granulation tissue.**
- **In addition to describing events of acute pancreatitis as adverse events of interest, also provide data on serum amylase and lipase (including reference range) and imaging results obtained in patients with suspected or confirmed pancreatitis.**
- **For infections, include an analysis of organism type (e.g., bacterial, fungal, viral, other).**

12. Does the Agency agree with types of narratives that Takeda proposes to include in the NDA resubmissions?

Response: Yes, we agree. Please provide links to the narratives in the study reports from summary tables and line listings.

13. Does the Agency find this submission plan acceptable and agree that submitting patient profiles in the NDA resubmissions is not necessary?

Response: Yes, we agree with your plan to submit subject narratives for the events agreed to in question 12 (b) (4).

14. Does the Agency agree with Takeda's proposal to not manufacture alogliptin/pioglitazone FDC dose strengths that contain alogliptin 6.25 mg and agree that the product labeling can appropriately address dosing patients with severe renal impairment through co-administration of alogliptin and pioglitazone tablets?

Response: Yes, we agree.

15. Does the Agency agree that the proposed analyses and table shells for the IAS and interim analysis are appropriately designed to evaluate the safety of alogliptin in subjects with renal impairment?

Response: The analyses and proposed data presentation are acceptable.

16. With regard to the analysis of adverse events by baseline and endpoint renal status for the IAS and final analysis for Study 402, Takeda defines endpoint renal status as the subject's renal status at the time of last renal assessment. Therefore, for this analysis adverse events will be summarized according to renal impairment (normal, mild, moderate, and severe or ESRD) at Baseline and according to renal impairment at the last renal assessment. Does the Agency agree with this definition of endpoint for this analysis?

Response: The proposed analyses are acceptable.

17. In the FDA Advice/Information Request letter dated 15 July 2009 regarding Study 402, the Agency stated that if a substantial percentage of patients experience a change in severity status during the course of the study, a secondary analysis should be conducted by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured. Takeda would like clarification on what percentage of patients experiencing a change in severity status during the course of the study would require Takeda to conduct the analysis based on renal severity status at endpoint for the final analysis.

Notes from internal meeting: We talked about a "substantial percentage" being 25-30%, with the understanding that approximately 400 to 500 subjects with moderate renal impairment and 100 severe renal impairment will be enrolled in study 405 and exposed to alogliptin for at least one year (see p. 23/36, section 2.2.2.3). From a statistical perspective, this would give a reasonable number of patients who progressed from moderate to severe renal impairment from which to summarize the percentage of adverse events of interest. However, this suggestion is certainly open to discussion.

Response: If ≥25% of patients experience a change in severity status during the course of the study, you should conduct the analysis based on renal severity status at endpoint for the final analysis.

18. Does the Agency agree with Takeda's proposal (b) (4)

Response: No, we do not agree. The proposal (b) (4) will be a review issue.

(b) (4)

20. Similar to the review timelines described in the Guidance document, Good Review Management Principles and Practices for PDUFA Products, Takeda would like to confirm that the Agency will plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Response: Should results from your application support approval, we plan to initiate labeling discussions at least 4 weeks prior to the scheduled action dates for each product.

Question 21: If the alogliptin and alogliptin/pioglitazone NDA resubmissions are submitted simultaneously, Takeda would like to confirm that a concurrent action will be taken by the Agency on both of these applications.

Response: If both NDAs are resubmitted at the same time, they will be on the same review clock and will have the same user fee goal date. A concurrent action is likely, but the possibility exists that the actions taken will not be concurrent.

Question 22: Takeda would like to obtain feedback regarding the need for an Advisory Committee meeting in light of the 6-month review cycle for Complete Response Submissions and the Agency's prior full review of alogliptin. Can the Agency comment at this time if an Advisory Committee meeting will be necessary?

Response: This decision will be made after the resubmission of these NDAs.

23. If Takeda notifies the Agency 4 months prior to submitting the NDA resubmissions, would the Agency be willing to initiate the process for re-review of 'Nesina' and '[redacted] (b) (4) at that time? If the Agency agrees with this proposal, would the Agency be able to conduct the re-review and confirm the acceptability of the proprietary names within a reasonable timeframe (e.g. 4 weeks)?

Note: The proposed proprietary names, 'Nesina' for alogliptin and '[redacted] (b) (4) for alogliptin/pioglitazone FDC, were found acceptable by the Agency during the first-cycle review of the alogliptin and A/P NDAs, although they must be re-reviewed following the NDA resubmissions of both applications.

Response: The Division of Medication Error Prevention and Analysis (DMEPA) reviews trade names. You should submit a request for trade name review when the complete response is submitted. DMEPA's review timeline is 90 days from the date the request is received.

Question 24: If Takeda decides to pursue different trade names for alogliptin and/or the A/P FDC product for launch, could Takeda submit such names for the Office of Surveillance and Epidemiology (OSE) to review and approve? For trade names that are subject of an NDA resubmission, what are the internal timelines associated with its review and approval?

Response: In the NDA resubmission, you may submit two different trade names for DMEPA to review. DMEPA's review timeline is 90 days from the date they receive the request. This review is generally finalized 90 days prior to the action date. If you wish to pursue alternate names, you will need to withdraw the names that were found to be conditionally acceptable and submit a request for review of the alternate names. This review will follow the same timelines as above.
Please also refer to the Guidance for Industry entitled "*Contents of a Complete Submission for the Evaluation of Proprietary Names*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf).

25. Does Agency agree that the pediatric clinical studies as described above will satisfy the requirements of PREA for alogliptin?

Response: We cannot comment on whether or not your proposed pediatric study will satisfy the requirements of PREA until the NDA is resubmitted and your

proposal is discussed with the Pediatric Review Committee (PeRC). However, we have some concerns with your proposed Phase 3 pediatric study such as:

(b) (4)

26. Takeda would also like to obtain feedback from the Agency regarding the utility of the proposed pediatric plan to qualify for exclusivity under the Best Pharmaceuticals for Children Act (BPCA). A revised Proposed Pediatric Study Request under Section 505A and BPCA will be submitted under separate cover following approval.

Response: We cannot into an agreement regarding a written request until after NDA approval.

<u>Other FDA Comments</u>:

1. **When presenting changes from baseline in laboratory parameters (e.g., Table 15.3.4.5.2) include change from baseline to the last available on-treatment measurement (intent-to-treat with last-observation-carried-forward)**
2. **It appears that the integrated analyses will use MedDRA version 12.0. If earlier versions of MedDRA were used for the individual study reports, include a table showing those preferred terms that were coded to new preferred terms as a result of the MedDRA version change.**

Appendix 1. Summary of foreign clinical studies (Reproduced from the sponsor)

Study No.	Study Design, Population, Treatment Duration
SYR-322-4833/CPH-001	**Design:** Phase 1, open-label, randomized 2-period crossover study to determine the bioequivalency of alogliptin and AD-4833 tablets when administered as individual tablets and as combination product and to determine the effect of food on the pharmacokinetics of combination product. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** Single-dose.
SYR-322-4833/CPH-002	**Design:** Phase 1, Open-label, randomized 2-period crossover study to determine the bioequivalency of alogliptin and AD-4833 tablets when administered as individual tablets and as combination product and to determine the effect of food on the pharmacokinetics of combination product. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CPH-003	**Design:** Phase 2, open-label study to assess the effect of age on pharmacokinetics, safety and pharmacodynamics of a single-dose of alogliptin in healthy elderly and non-elderly adult male subjects. **Population:** Japanese healthy male subjects; aged 65 to 85 years for elderly subject or aged 20 to 35 years for non-elderly subject, inclusive. **Treatment Duration:** Single-dose.
SYR-322/CPH-004	**Design:** Phase 2, open-label study to assess the effect of voglibose on the pharmacokinetics of alogliptin. **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CPH-007	**Design:** Phase 2, open-label, randomized, crossover study to determine the food effect on the pharmacokinetics, pharmacodynamics, safety and tolerability of single dose of the commercial alogliptin tablets (12.5 and 25 mg). **Population:** Japanese healthy male subjects; aged 20 to 35 years, inclusive. **Treatment Duration:** 2 days.
SYR-322/CCT-001	**Design:** Phase 2, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin. **Population:** Men or women, 20 years of age or older, with T2DM and inadequate glycemic control on diet and exercise alone. **Treatment Duration:** 12 weeks.
SYR-322/OCT-001	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-001). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the phase 2 dose-ranging study).
SYR-322/CCT-003	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of SYR-322 when used in combination with α-glucosidase inhibitor. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-001). **Treatment Duration:** 24 weeks.
SYR-322/OCT-003	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with α-glucosidase inhibitor in subjects with T2DM. **Population:** The subjects who have completed the phase 2 dose-ranging study (SYR-322/CCT-003). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 α-glucosidase inhibitor add on study).

Study No.	Study Design, Population, Treatment Duration
SYR-322/CCT-004	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with thiazolidinedione **Population:** Men or women, 20 years of age or older, with T2DM and inadequate glycemic control on pioglitazone as well as diet and exercise **Treatment Duration:** 12 weeks
SYR-322/OCT-004	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with thiazolidinedione. **Population:** The subjects who have completed the phase 2/3 thiazolidinedione add on study (SYR-322/CCT-004). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 thiazolidinedione add on study).
SYR-322/CCT-005	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with sulfonylurea. **Population:** Men or Women, 20 years of age or older, with T2DM and inadequate glycemic control on sulfonylurea as well as diet and exercise. **Treatment Duration:** 12 weeks.
SYR-322/OCT-005	**Design:** Long-term, open-label extension study to investigate the long-term safety of alogliptin when used in combination with sulfonylurea and/or metformin. **Population:** The subjects who have completed the phase 2/3 sulfonylurea add on study (SYR-322/CCT-005) or biguanide add on study(SYR-322/CCT-006). **Treatment Duration:** 40 weeks (52 weeks from the start of treatment in the core phase 2/3 sulfonylurea add on study or biguanide add on study).
SYR-322/CCT-006	**Design:** Phase 2/3, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of alogliptin when used in combination with metformin. **Population:** Men or Women, 20-64 years of age, with T2DM and inadequate glycemic control on biguanide. **Treatment Duration:** 12 weeks.

Appendix 2. Proposed structure of the alogliptin NDA resubmission (Reproduced from the sponsor)

Module	Section	New or Updated Information
1		• Updated draft product label. • All applicable updated regional information.
2	2.4	• Updated nonclinical overview.
	2.5	• Updated clinical overview.
	2.6.6	• Additional nonclinical written summaries including range-finding and embryo-fetal development studies.
	2.6.7	• Additional nonclinical tabular summaries including range-finding and embryo-fetal development studies.
	2.7.1	• Pharmacokinetic data from Studies 101 and 103.
	2.7.3	• Efficacy data from Studies 301, 303, OPI-001, OPI-002, and OPI-004.
	2.7.4 (a)	***Part 1: Summary of Safety by Individual Study*** • MACE analyses and an overall safety evaluation from Study 402. • Safety data from Studies 101, 103, 301, 303, OPI-001, OPI-002, and OPI-004 and foreign studies. • Updated SAE summary table for Study 012 (since the alogliptin 120-day safety update). ***Part 2: Integrated Safety Analyses of Controlled Clinical Studies*** • Pooled MACE analysis of all controlled phase 2 and 3 studies. • Safety update evaluating a pooled analysis of all phase 2 and 3 controlled studies (adding studies 402, 301, 303, OPI-001, OPI-002, and OPI-004). • Long-term safety evaluation from 1-year controlled studies 303, 402, and OPI-004.
	2.7.5	• List of new references cited in 2.7.
	2.7.6	• Synopses for Studies 101, 103, 301, 303, OPI-001, OPI-002, and OPI-004.
4		• Nonclinical study reports including the range-finding and embryo-fetal development studies.
5	5.2	• Updated table of clinical studies.
	5.3	• Clinical study reports for Studies 101, 103, 301, 303, and OPI-004 (OPI-001 and OPI-002 were previously submitted in the alogliptin NDA) and foreign studies. • Narratives for Study 402, any requested narratives not included in the clinical study reports for Studies 101, 103, 301, 303, and OPI-004, and SAE narratives for Study 012. • Tables, listings, and graphs for Study 402 and the integrated analyses. NOTE: The integrated analyses will be summarized in Module 2.7.4 and not repeated as a separate report in this module.
	5.4	• Copies of new references.

(a) Module 2.7.4 from NDA 22-426 for alogliptin/pioglitazone FDC will also be submitted to NDA 22-271 for alogliptin.

Appendix 3. Proposed structure of the A/P NDA resubmission (Reproduced from the sponsor)

(b) (4)

Appendix 4. Study protocol SYR-322_307: An international, multicenter, randomized, double blind, placebo controlled, metformin-referenced study to evaluate the efficacy and safety of alogliptin compared with placebo in subjects aged 10 to 17 years with type 2 diabetes (Reproduced from the sponsor)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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

/s/

VALERIE S PRATT
02/24/2010

HYLTON V JOFFE
02/24/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 069707

MEETING MINUTES

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

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

We also refer to the teleconference between representatives of your firm and the FDA on January 14, 2010. The purpose of the meeting was to discuss the feedback that we provided in a letter dated January 4, 2010, regarding your cardiovascular outcomes protocol.

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of meeting minutes from teleconference held on January 14, 2010

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	January 14, 2009, 11:00 AM – 12:00 PM (Eastern)
Meeting Location:	Teleconference
Application Number:	IND 069707
Product Name:	Alogliptin tablets
Indication:	Treatment of type 2 diabetes mellitus
Sponsor/Applicant Name:	Takeda Global Research & Development Center, Inc.
Meeting Chair:	Ilan Irony, M.D.
Meeting Recorder:	Mehreen Hai, Ph.D.

FDA ATTENDEES

Ilan Irony, M.D.	Diabetes Team Leader, Division of Metabolism & Endocrinology Products (DMEP)
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Penny Fleck, M.T.	Director, Clinical Science
Neila Smith, M.D.	Senior Medical Director, Pharmacovigilance
Mick Roebel, Ph.D.	Senior Director, Regulatory Affairs
Christie Idemoto, M.S.	Manager, Regulatory Affairs

1.0 BACKGROUND

On September 17, 2004, Takeda Global Research & Development (TGRD) submitted IND 069707 for alogliptin (SYR-322) tablets, a dipeptidyl-peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes mellitus. On December 27, 2007, TGRD submitted NDA 22-271 for alogliptin. On June 26, 2009, the Agency issued a Complete Response letter for NDA 22-271.

The Agency issued the Guidance for Industry entitled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" in December 2008.

On July 29, 2009, TGRD submitted revisions to Protocol SYR-322_402, entitled: "*A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment with Alogliptin in Addition to Standard of Care in Subjects with Type 2 Diabetes and Acute Coronary Syndrome*". On September 11, 2009, TGRD also submitted the Case Report Form, the Data Monitoring Committee Charter and the updated Standard of Care Guidelines document in support of Study SYR-322_402. The Division reviewed these submissions and provided comments in a letter dated January 4, 2010. On January 11, 2010, TGRD submitted a meeting request to discuss and clarify the Division's feedback regarding their CV outcomes protocol and related submissions. This meeting request was granted and a teleconference was scheduled for and held on January 14, 2010.

2. DISCUSSION

The Sponsor requested discussion of certain points in the letter issued by the Division on January 4, 2010. The contents of the letter are repeated below and a summary of the meeting discussion follows the sections that were discussed in italicized font. The sections of the letter that were not discussed at the teleconference are also included without an accompanying meeting discussion section.

In reference to Protocol SYR-322_402:
Clinical comments:

1. In **Appendix E: Inclusion Criteria Definition for Acute Coronary Syndromes** (page 54 of 139), you have proposed an Inclusion Criterion Definition for hospitalization for unstable angina.
   a. Per the American College of Cardiology 2007 Guidelines for the Management of Patients with Unstable Angina/Non ST-Elevation Myocardial Infarction: Executive Summary (Circulation 2007; 116;803-877, page 821), unstable angina is defined as having "no biomarkers in circulation." Please clarify whether the definition above will require negative cardiac biomarkers.

Meeting discussion: TGRD explained that they do not plan to revise their protocol to include negative cardiac biomarkers. The Division stated that this was acceptable.

b. With respect to Bullet 3: "Evidence for prior coronary artery disease by cardiac catheterization.", it seems unlikely that subjects found to have luminal irregularities (10-20% stenosis) by cardiac catheterization would be likely to be hospitalized for unstable angina. Furthermore, if all subjects underwent intravascular ultrasound examination, all subjects would likely have some degree of coronary artery disease. Modify this proposed definition to make it more specific and likely to reflect true unstable angina.

Meeting discussion: TGRD stated that they plan to modify the definition to: "Evidence for prior coronary artery disease by cardiac catheterization with documentation of significant stenosis". The Division stated that this was acceptable.

c. Bullets 1, 2 and 4 appear to be reasonable.

2. In **Appendix H: Cardiovascular Event Checklist** (page 139 of 139), we recommend a drop-down box for types of death.

3. **Section 10.2.5: Additional Information for Adjudication of Potential CV Events** (page 114 of 139) specifies how the adjudicated events will be categorized. Clarify that although all hospitalization for unstable angina will be adjudicated, unstable angina requiring urgent revascularization only is a component of the secondary composite endpoint.

4. **Renal Safety Endpoints and Renal Stopping Criteria:** You propose measuring eGFR at baseline, Month 1 (Visit 3), Month 6 (Visit 5), Month 12 and q 4 months thereafter. However, we recommend that you also measure eGFR at Month 3 (Visit 4).

5. **Liver Safety Monitoring and Withdrawal Criteria:** Your proposed liver safety monitoring and withdrawal criteria state study medication will be "interrupted" if ALT or AST >8x ULN OR =3x ULN in conjunction with bilirubin >2x ULN. Clarify if you intended "≥3x ULN" rather than "=3x ULN".

   Clarify in which subjects and at what approximate frequency repeat liver tests will be drawn.

   You propose discontinuing treatment in subjects with ALT or AST >5x ULN for more than two weeks OR ALT or AST = 3 times ULN with the appearance of fatigue, nausea, vomiting, upper right-quadrant tenderness, fever, rash, or eosinophilia. Clarify if you intended "≥3x ULN" rather than "=3x ULN". Please also consider discontinuation of treatment in subjects with ALT or AST >8x ULN OR ALT or AST >3x ULN with total bilirubin >2x ULN or INR >1.5, as suggested in the Guidance for Industry (October 2007) entitled, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation." (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf).

Meeting discussion: TGRD stated that they plan to incorporate the changes suggested by the Division regarding Liver Safety Monitoring and Withdrawal Criteria.

6. Since stent thrombosis typically presents as CV death or myocardial infarction, which are components of the primary endpoint, we recommend that stent thrombosis in the study is clinically adjudicated using the Academic Research Consortium definition and that the timing of the events per treatment group is specified.

Meeting discussion: TGRD explained the difficulties of trying to adjudicate stent thrombosis. The Division stated that the clinical manifestations of stent thrombosis (CV death and myocardial infarction) should be adjudicated.

7. The protocol allows for one urine pregnancy test to be checked at baseline. Please check additional urine pregnancy tests during the course of the trial.

Meeting discussion: TGRD stated that they plan to conduct annual pregnancy tests. The Division stated that this was acceptable.

8. Submit the Randomization Code for each patient with the Clinical Study Report.

9. We recommend that you create investigator endpoint reporting forms and CEC adjudication forms for endpoint events for the study. Please submit these forms for review prior to study initiation.

Meeting discussion: TGRD explained that since adjudication forms are used by the CEC adjudication committee and Serious Adverse Event forms are used by the investigators, TGRD does not see the need for investigator endpoint reporting forms. The Division stated that this was acceptable.

10. Please submit a revised Protocol SYR-322_402 with all primary, secondary, and exploratory endpoint definitions as soon as possible. Please note that the CV definitions in Protocol SYR-322_402 and the CEC Charter should be identical.

Meeting discussion: TGRD explained that they prefer to retain the CV definitions in the CEC Charter, and not add them to the protocol, since a new protocol will need to be submitted and reviewed every time the definitions are modified. TGRD explained that the protocol specifies the events of interest that is relevant to the IRB and the investigators. The Division stated that this was acceptable, and reiterated that the investigators need to be aware of the endpoint events to report.

11. A recent study of sitagliptin and metformin in human islet amyloid polypeptide transgenic (HIP) rats, a model for type 2 diabetes, showed pancreatitis in one, ductal metaplasia in three, and increased ductal turnover in all sitagliptin-treated rats (*Matveyenko, AV et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes. Diabetes 2009, 58:1604-1615*). The effects reported were attributed to the sitagliptin inhibition of dipeptidyl peptidase-4. Since alogliptin and sitagliptin share this mechanism of action, subjects treated with alogliptin could be at risk for pancreatitis and/or pancreatic cancer. In studies with alogliptin, measure serum amylase and

lipase at baseline for all study participants, as well as in subjects with persistent (e.g. ≥3 days) nausea and/or vomiting with or without abdominal pain.

12. Pancreatic cancer should be analyzed as an adverse event of special interest in alogliptin studies ≥1 year, including cardiovascular outcomes trial SYR-322_402.

In reference to Protocol SYR-322_402:
Statistical comments:

13. We agree with the proposed group sequential analysis, using an O'Brien-Fleming spending function, after 80, 100, 125 and 150 adjudicated events, to evaluate the non-inferiority of alogliptin to placebo with a non-inferiority margin of 1.8, a true hazard ratio of 1.0, and an overall 1-sided 2.5% significance level. We concur with the calculations of statistical power at this interim stage of the study.

14. We agree with the proposed group sequential analysis, to be conducted conditional on meeting the non-inferiority margin of 1.8 but not meeting the non-inferiority margin of 1.3 after 150 adjudicated events. The proposed group sequential analysis will be conducted with an O'Brien-Fleming spending function, after 550, 600, and 650 adjudicated events, to evaluate the non-inferiority margin of 1.3, a true hazard ratio of 1.0, and an overall 1-sided 2.5% significance level. We concur with the calculations of statistical power at this interim stage of the study.

In reference to the updated Standard of Care Guidelines:

15. Since care guidelines seem to be substantially different between Eastern European countries (e.g., Poland, Bulgaria, Ukraine) and the United States, please make sure that your trial enrolls at least 30% of subjects from the United States to ensure that study results will be generalizable to the US population.

In reference to the Charter for the Data Monitoring Committee (DMC) for Alogliptin Cardiovascular Outcomes Study SYR322_402 (page 6):

16. The Data Monitoring Committee has five core members, none of whom are neurologists. Since stroke is a component of the primary composite endpoint, we recommend that a neurologist adjudicator is also appointed to the DMC.

Meeting discussion: TGRD explained that the Data Monitoring Committee is responsible for safety oversight, and therefore a neurologist is not required on this committee. The CEC Adjudication Committee does have a neurologist member. The Division stated that this was acceptable.

In reference to the Case Report Form (CRF):

17. Please insert page numbers.

18. Concomitant Medications:
    - Please include fields that reflect whether a concomitant medication has been temporarily interrupted (dates of interruption) as well as the reason for interruption of medication. This information is especially important with respect to the use of thienopyridine, aspirin, and proton pump inhibitors.
    - Some concomitant medications may not be taken daily - incorporate a mechanism into your CRF to capture actual dosing of concomitant medication (qd, bid, prn etc.).
    - Capture whether or not a female subject is on hormone replacement therapy or oral contraceptives.

Meeting discussion: TGRD explained the difficulties of obtaining the reason for interruption of concomitant medications. The Division concurred that collection of this data was not necessary. Secondly, TGRD explained that the dosing data was likely to be more accurate if it was collected in the context of total daily dose. The Division stated that this was acceptable. Finally, TGRD stated that they plan to capture whether a female subject is on hormone replacement therapy or oral contraceptives.

19. Pretreatment Event/Adverse Event: Include the time for start date and stop date.

Meeting discussion: TGRD explained the difficulties of capturing the time for start and stop date of pretreatment events and adverse events. The Division concurred that this was not necessary.

20. Serious Adverse Events: Record the time with admission date and discharge date.

Meeting discussion: TGRD explained that although they do plan to collect the time for serious adverse events, they do not plan to present this data unless requested to do so. The Division stated that this was acceptable.

21. Dosing: Record time of first dose of double blind study drug (in addition to the already specified date).

Meeting discussion: TGRD explained the difficulties of capturing the time of first dose of double blind study drug. The Division concurred that this was not necessary.

22. Renal Dialysis Status: Since adverse events can occur during dialysis, record times as well as the dates of renal dialysis.

Meeting discussion: TGRD explained the difficulties of capturing the time of renal dialysis. The Division concurred that this was not necessary.

23. Demography
    - Record weight in kilograms at baseline, in addition to other specified times during the study at the time of other Vital Signs.

- Instead of having separate fields for Ethnicity and Race, consider having one field for ethnic origin and including Hispanic or Latinos as one of the options here.
- Smoking History: Record the number of years the subject smoked in addition to recording the proposed smoking classification (never smoked, current smoker, ex-smoker).

Meeting discussion: TGRD explained that they plan to follow the suggestion regarding recording of weight. Secondly, TGRD explained that the Ethnicity and Race fields were consistent with ICH guidelines. Finally, TGRD explained that they plan to follow the suggestion to record the number of years the subject smoked.

24. Cardiovascular History: In addition to asking about a history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention (PCI) (terminology typically used today as opposed to percutaneous transluminal coronary angioplasty (PTCA), unstable angina, peripheral artery disease, hypertension, and hyperlipidemia please also record the following medical history/pertinent physical exam findings:

- whether or not the subject had prior PCI at the target lesion site responsible for symptoms qualifying enrollment in trial (e.g. restenosis) – *TGRD plans to add this.*
- whether or not the subject had prior PCI at a remote site – *TGRD plans to add this.*
- whether or not the subject had a prior cerebrovascular accident (stroke) – *TGRD plans to add this.*
- whether or not the subject had a prior transient ischemic attack – *TGRD plans to add this.*
- atrial fibrillation (would record this field as opposed to the proposed cardiac arrhythmia field) – *TGRD plans to add this.*
- family history of premature coronary artery disease – *The Division concurred with TGRD that this is not necessary, as it would be difficult to obtain accurately.*
- hyperlipidemia
- hypertriglyceridemia
- low HDL (women < 50 mg/dL, men < 40 mg/dL)

– TGRD explained that they plan to capture the previous three items by means of a lipid panel at baseline and a record of lipid-related medications. The Division stated that this was acceptable.

- carotid/vertebral arterial disease – *TGRD plans to add this.*
- diabetes (and how treated/duration of condition) (defer to DMEP on specifics) – *The Division concurred with TGRD that details of the treatment are not necessary to collect, as this would be difficult to obtain accurately.*
- peptic ulcer disease – *The Division concurred with TGRD that this is not necessary.*
- presence of rales on physical examination (yes/no)
- peripheral edema on physical examination (yes/no) and if yes, degree of edema

– TGRD explained that they plan to record the previous two items, if present, but the degree of edema was too subjective to capture. The Division concurred.

- pacemaker placement and if so, reason for placement - *TGRD explained that they plan to record pacemaker placement, but the reason for placement was likely to be inaccurate. The Division concurred with TGRD that this is not necessary.*

- automatic implantable cardioverter-defibrillator and date of implantation
- cardiac resynchronization therapy (biventricular pacemaker) and date of implantation

– *TGRD explained that they do not plan to record date of implantation for the previous two items. The Division stated that this was acceptable.*

- history of ablation (and specify dysrhythmia) - *TGRD explained that they plan to record this as past medical history.*

Meeting discussion: TGRD and the Division discussed each of the points above, as detailed following each point.

25. Medical History: Please specifically query the subject about a past history of cancer and record date, site, treatment (radiation, surgical excision, chemotherapy, oral hormone therapy, multiple treatments, etc.), and whether or not the cancer is currently being treated. If possible, record histopathology information.

- If a death is due to a malignancy, ensure that the endpoint reporting form includes information as to whether or not this is a new malignancy or a worsening malignancy.
- Obtain the Medwatch Form/narrative description of the event, autopsy report, and pathology reports.

Meeting discussion: TGRD explained that while they will attempt to ascertain past history and treatment of cancer, this is likely to be inaccurate, especially in the details. TGRD also explained that there is difficulty in concluding whether or not death was due to malignancy. The Division acknowledged these difficulties, and suggested that TGRD do what is reasonably possible.

26. Laboratory Samples:

- Define what constitutes a clinically significant lab abnormality (if you have an electronic CRF, you may wish to have a drop-down menu).
- Record dates and times of laboratory samples and date as well as time of the pharmacogenomic samples collected.
- Record date and time of urine pregnancy test(s).
- Record upper and lower reference limits for laboratory samples.
- With respect to troponin assays, please record the upper reference limit (for myocardial necrosis) as well as the lower reference limit.
- Record whether or not laboratory samples were centrally or locally run.

Meeting discussion: TGRD explained that they have a central laboratory that tests the protocol-related laboratory samples, other than those that are taken and tested at the time of an event that most likely occurs in a different medical facility. TGRD explained that they do not plan to record times for the protocol-related lab samples. The Division stated that this was acceptable, with the exception of lab samples related to endpoint events, where it would be useful to record the time of the event and the collection of the lab sample.

27. First Assessment 12-Lead Electrocardiogram (ECG) and all other 12-lead Electrocardiograms:

- Record time of 12-lead ECG, in addition to date.
- We suggest that in addition to pertinent Q-waves you also record pertinent ST elevation, ST depression, and T-wave changes—please refer to DMEP draft definition for myocardial infarction.
- Record whether or not there is a new, or presumed new, left bundle branch block.

Meeting discussion: TGRD explained that the time of the ECG would be collected and used for narratives. The Division stated that this was acceptable.

28. Eligibility: Record the date as well as time of randomization.

Meeting discussion: TGRD explained that they do not plan to collect the time of randomization of the clinical database. The Division stated that this was acceptable.

29. End of Study Drug: Record the time.

Meeting discussion: TGRD explained that they do not plan to collect the time of End of Study Drug. The Division stated that this was acceptable.

30. End of Study Visits: Record the time.

Meeting discussion: TGRD explained that they do not plan to collect the time of End of Study Visits. The Division stated that this was acceptable.

31. Clarify whether or not you plan to record non-serious adverse events, as no CRF forms for these events were provided.

Meeting discussion: TGRD explained that they plan to capture non-serious adverse events in the case report form.

Post-Meeting FDA Comment: We refer to your submission dated October 14, 2009, containing the CEC Charter and Adjudication Worksheet related to your cardiovascular outcomes protocol. We have completed our review of this submission and find it acceptable.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

4.0 ACTION ITEMS

(a) TGRD will submit a revised cardiovascular outcomes protocol and case report form, and include in their submission a written response to the information requested in letter issued by the Division on January 4, 2010.

(b) The Division will complete its review of the CEC Charter and Adjudication Worksheet submitted by TGRD on October 14, 2009, and provide comments to TGRD *[included here with the meeting minutes]*.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-69707	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	SYR-322 TABLETS

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

/s/

MEHREEN HAI
02/10/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271
NDA 022426

MEETING GRANTED

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets and for (b) (4) (alogliptin/pioglitazone fixed-dose combination) Tablets.

We also refer to your October 28, 2009, correspondence requesting an End-of-Review conference to discuss and confirm the steps required to support the approvability of NDA 022271 and NDA 022426. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date:	**Tuesday, February 23, 2010**
Time:	**1:30 – 3:00 pm**
Location:	**FDA White Oak Campus, Building 22** **10903 New Hampshire Avenue, Silver Spring, MD 20993**

CDER participants (tentative):

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II (ODE II)
Lee Ripper	Associate Director for Regulatory Affairs, ODE II
Mary Parks, M.D.	Director, Division of Metabolic and Endocrinology Products (DMEP)
Hylton Joffe, M.D.	Diabetes Team Leader, DMEP
Valerie Pratt, M.D.	Clinical Reviewer, DMEP
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Suong Tran, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-marketing Assessment I
Sally Choe, Ph.D.	Team Leader, Division of Clinical Pharmacology II
Sang Chung, Ph.D.	Reviewer, Division of Clinical Pharmacology II

Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Janice Derr, Ph.D.	Statistics Reviewer, Division of Biometrics II
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Mehreen Hai (796-5073); Penya Littleton (796-1180).

Please notify me at least two weeks prior to the meeting if any of your attendees are NOT U.S. citizens, as additional information will be required.

Provide the background information for the meeting (three copies to the application and **20** desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by January 22, 2010, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS
NDA-22426	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	ALOGLIPTIN/PIOGLITAZONE TABLET

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

/s/

MEHREEN HAI
12/15/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-271
IND 69,707

GENERAL ADVICE

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

We also refer to your submission dated August 31, 2009, containing comments regarding the minutes that were issued on August 26, 2009, for the meeting between representatives of your firm and the FDA held on April 27, 2009. The purpose of the meeting was to discuss your proposed cardiovascular outcomes trial with alogliptin (Protocol SYR-322_402, entitled: "*A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment with Alogliptin in Addition to Standard of Care in Subjects with Type 2 Diabetes and Acute Coronary Syndrome*", submitted on July 29, 2009).

We have reviewed your comments and are providing responses. The meeting minutes are repeated below in normal font. You have provided comments for Questions 1, 2, 6, 9, 11, 13, 14, and 17, and Additional Comments 2 and 7. Your comments are in bold font. Our response to each comment follows in bold, italicized font.

Protocol Design

1. Does the Agency agree that the protocol is appropriately designed to assess the CV risk associated with alogliptin?

   FDA Pre-Meeting Response: The Division provides preliminary comments below. Additional comments may be forthcoming after the Division has reviewed the updated, complete protocol (which should include definitions for all endpoints of interest and the adjudication committee charter).

   While the Division recognizes that the December 2008 Guidance to Industry Diabetes Mellitus – Evaluating CV Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes Mellitus discusses the possibility of including CV events other than CV death, MI, and stroke, the Division encourages a more traditional MACE composite of CV death, nonfatal

myocardial infarction, and nonfatal stroke. The Division recommends a more traditional MACE endpoint (b) (4) Should the Sponsor proceed with the proposed composite endpoint, the contribution of each component of the composite endpoint to the overall efficacy findings will be a consideration to whether the Sponsor has ruled out an unacceptable cardiovascular risk associated with alogliptin.

With respect to stroke, the Division recommends classifying the event as ischemic (non-hemorrhagic), hemorrhagic, or unknown, and the Division recommends classifying stroke severity according to the modified Rankin Scale.

Furthermore, the Division recommends examining hospitalization for unstable angina (with or without urgent revascularization), hospitalization for congestive heart failure, all cause mortality, stent thrombosis, hospitalization for other cardiovascular causes, and lower extremity amputation, primarily due to ischemia, as secondary endpoints in addition to the secondary endpoints the Sponsor has already proposed of CV death, nonfatal MI, and nonfatal stroke. Hospitalization for other cardiovascular causes would include pulmonary embolism, ruptured aortic aneurysm, and arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement).

Meeting Discussion: The Sponsor agreed with the recommendation to (b) (4)

The Sponsor said that it may not be feasible to classify stroke severity on the Rankin Scale because there may not be enough information in the inpatient records. However, the Sponsor will take the recommendation under advisement.

The Division stated that the Agency is in the process of standardizing the definitions for cardiovascular endpoints. The recommendations included in the preliminary responses represented the Division's thinking at the time of the meeting (please see the Post-Meeting Comment below for updated recommendations).

The Sponsor presented a slide (see attached slide #3) of the proposed secondary endpoints. It is acceptable for the Sponsor to analyze various composites of cardiovascular endpoints as secondary endpoints; however, the Division stated that the Sponsor should also evaluate the cardiovascular endpoints individually as secondary endpoints.

The Sponsor stated that investigators will be encouraged to manage patients based on regional guidelines. The Sponsor plans to submit to the Division a document with regional guidance, which will be separate from the protocol. The Sponsor will document that investigators are trained based on the regional guidance and any changes to the regional guidance will be tracked by the Sponsor. The Division stated that this is acceptable.

The Sponsor will provide the adjudication charter for review.

Post-Meeting Comment: The Division is further along in the process of standardizing recommendations and definitions for cardiovascular endpoints for use by all sponsors who are developing treatments for type 2 diabetes. See the attached appendices for the most recent version of these documents. Note that the cardiovascular endpoint definitions have not been finalized. Pharmaceutical Research and Manufacturers of America (PhRMA) is in the process of testing the workability of these definitions. Based on the results of this testing, additional modifications may be forthcoming.

The Division acknowledges subsequent discussions with the Sponsor regarding the design of the cardiovascular trial since this Type A meeting, including discussions related to the inclusion criteria (see Post-Meeting Comment under Question 2), the primary endpoint, and the statistical analysis plan. In subsequent telephone conferences on June 3, 2009 and July 10, 2009, the sponsor proposed including (b) (4) (b) (4) Therefore, the Division recommended that the primary endpoint include cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke only (b) (4) Should the Sponsor proceed with a primary composite endpoint (b) (4), the contribution of this component of the composite endpoint to the overall findings would be a consideration as to whether the Sponsor had ruled out unacceptable cardiovascular risk with alogliptin. The Division acknowledges the sponsor's recent submission of the amended clinical protocol for the cardiovascular trial. Additional comments may be forthcoming after our review is completed.

TGRD Comment:
• Under Post-Meeting Comment, the dates that TGRD and the Agency held subsequent teleconferences regarding the primary endpoint were on May 27, 2009 and July 10, 2009 (rather than June 3, 2009 and July 10, 2009).

FDA Response to TGRD Comment: Yes, we agree with the revised dates.

2. Does the Agency agree that the higher risk T2DM population chosen for this study is appropriate?

FDA Pre-Meeting Response: Yes, the Division agrees that the higher risk type 2 diabetes population chosen for this study is appropriate. However, (b) (4) the Division recommends randomizing patients with a diagnosis of ACS 2-4 weeks after the index ACS event, because many cardiovascular endpoints in this population occur early.

Meeting Discussion: The Sponsor proposed randomizing patients 15 to 60 days following a diagnosis of ACS. This would allow the physician to stabilize the patient and still be able to randomize the patient. The Division stated that the Sponsor's proposal is reasonable.

The Sponsor presented a slide (see attached slide #4) with the justification for a revised sample size. The post-ACS event rate was re-estimated at 6% because of the changed criterion. The Division stated that this seems reasonable.

Post-Meeting Comment: Since the Meeting on April 27, 2009, there has been further internal discussion within FDA about cardiovascular trial designs for treatments developed for diabetes. At a meeting between members of the Division of Cardio-Renal Products and the Division of Metabolism and Endocrinology Products on May 11, 2009, the general consensus was not to enroll patients with ACS prior to 2 months from the index event because all of the early events could add noise to the overall trial and bias towards showing non-inferiority.

As a result, in a telephone conference with the sponsor on June 3, 2009, we recommended enrolling patients with ACS at least 2 months after the index event, which would likely change the sample size and trial duration. In addition to enrolling patients with ACS and renal insufficiency, we recommended enriching the trial with patients having other high risk characteristics too, in order to make the result of the cardiovascular outcomes trial more generalizable.

Despite these potential limitations, the sponsor still wishes to keep the inclusion criterion as 15-60 days following a diagnosis of ACS. The Division of Metabolism and Endocrinology Products stated this will be acceptable; however, if there are many early events, the adequacy of the findings will be a review issue.

TGRD Comment:

• The summary provided under Post-Meeting Comment is not an accurate reflection of the discussions that took place following the April 27, 2009 Type A meeting. At the July 10, 2009 teleconference, the Division stated that the proposed study population (i.e. patients with a diagnosis of acute coronary syndrome (ACS) within 15 days to 6 months prior to randomization) will be acceptable. TGRD would like the final clause which states, "however, if there are many early events, the adequacy of the findings will be a review issue", to be removed as this was not stated by the Division.

To capture the discussion accurately, TGRD suggests that the final paragraph under Post-Meeting Comment be revised to state the following:

(b) (4)

FDA Response to TGRD Comment: ***No, we do not agree. We did state that your proposal to keep the inclusion criterion as 15-60 days following a diagnosis of ACS will be acceptable, but we also stated that if there are many early events, the adequacy of the findings will be a review issue. The reason for this caveat is that patients who are enrolled after a very recent cardiovascular event are at risk for early recurrent events that***

are independent of treatment assignment. Many such events may bias results towards non-inferiority. Nevertheless, if you wish to change the inclusion criterion to subjects with a diagnosis of ACS within 15 days to 6 months prior to randomization, this change would be acceptable, but we recommend that you plan on doing a subgroup analysis to evaluate the primary and secondary endpoints according to subjects with an ACS event ≤ 2 months versus subjects with an ACS event > 2 months prior to randomization. Still, if there are many early events, the adequacy of the findings will be a review issue.

TGRD Comment:
• Under Post-Meeting Comment, the date that TGRD and the Agency held a subsequent teleconference regarding the patient population was on May 27, 2009 (rather than June 3, 2009).

FDA Response to TGRD Comment: Yes, we agree with the revised date.

Study Endpoints

3. Does the Agency agree with the proposed primary endpoint of time from randomization to the first occurrence of any of the events in the primary MACE composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina (with or without urgent revascularization)?

   FDA Pre-Meeting Response: Refer to the response to Question 1.

   Meeting Discussion: None

4. Does the Agency agree that the secondary endpoint adequately supports the primary endpoint?

   FDA Pre-Meeting Response: Refer to the response to Question 1.

   Meeting Discussion: None

General Safety Evaluation

5. Does the Agency agree with the safety data that Takeda plans to collect and analyze in the proposed CV outcomes study?

   FDA Pre-Meeting Response: No, the Division does not agree. Although targeted questions can be used to capture adverse events (AEs), the Division recommends that investigators use check boxes to query patients and to report cardiovascular adverse events of interest. This event reporting will trigger review by the Clinical Events Committee (CEC). Emergency Room, hospital, and revascularization (percutaneous coronary intervention, coronary artery bypass grafting, peripheral) reports and amputation operative reports, 12-lead

electrocardiograms (ECGs), and laboratory results will need to be obtained for review by the CEC for the endpoints described in Question 1 contributing to the primary and secondary endpoints.

Additionally, if a patient is hospitalized for acute coronary syndrome or revascularization procedures after randomization, serial cardiac enzymes (creatine phosphokinase [CPK], CK-MB, troponin) and 12-lead ECGs should be obtained per protocol.

Furthermore, it is essential that investigator "verbatim terms" be recorded and listed in the adverse events dataset submitted to the Agency with the Clinical Study Report, along with lower level terms, preferred terms, and system organ classes (SOCs) to which the verbatim term was originally coded. If there are any changes made to the verbatim terms, these changes must be documented as well as the reason for the changes, and this information should be submitted with the Clinical Study Report.

With the Clinical Study Report, the Division recommends that 5 patient listings be submitted:

- Listing of all investigator reported events
- Listing of all CEC adjudicated events
- Listing of all investigator reported events that were also adjudicated by the CEC to be events
- Listing of all investigator reported events that were downgraded as "non events" by the CEC
- Listing of CEC adjudicated events that were not thought to be events by the investigator and were not reported by the investigator

Women of childbearing potential should be educated to contact the investigator for a possible pregnancy test if changes in menstrual bleeding are observed.

The Sponsor should follow adverse events of angioedema and pancreatitis as events of special interest.

The trial should include prespecified renal safety endpoints.

Meeting Discussion: The Sponsor presented a slide (see attached slide #9) listing the adverse events to be collected. The Sponsor stated that all hospitalizations would be considered serious adverse events. The Sponsor will not use general open-ended questions to collect adverse events. The Division recommended using check-boxes for cardiovascular events, including revascularization procedures. The Sponsor stated that the check-boxes will serve as a trigger for investigators to complete case report forms for additional data.

The Division asked that the Sponsor include a list of renal safety endpoints in the protocol. The Sponsor presented a slide (see attached slide #10), listing the proposed renal safety endpoints. The Division agreed to provide comments on the renal endpoints after review of the full protocol. The Division asked whether the Sponsor will assess hepatotoxicity. The

Sponsor stated that the trial will include routine measurements of liver tests and will include stopping criteria based on liver test abnormalities.

Dose Selection

6. Does the Agency agree with the proposed dose selection for this study?

   FDA Pre-Meeting Response: Consider dose adjustment to 12.5 mg for patients with mild renal impairment due to a mean exposure increase of 69% in this patient population.

   Meeting Discussion: None

   TGRD Comment:
   • During the April 27, 2009 Type A meeting, the Division agreed that patients with mild renal impairment can be dosed with alogliptin 25 mg in this study. This was based on a written justification that was submitted to the Division on April 25, 2009, ahead of the face-to-face meeting.

   Consistent with the language used by the Division in an Advice/Information Request letter dated July 15, 2009, TGRD suggests the following under Meeting Discussion:

   "Meeting Discussion: The Division concurs that patients with mild renal impairment can be dosed with alogliptin 25 mg."

   FDA Response to TGRD Comment: Yes, we agree that patients with mild renal impairment can be dosed with alogliptin 25 mg in protocol SYR-322_402.

Evaluation of Subjects with Renal Impairment

7. Does the Agency agree that the proposed CV outcomes study can be used to provide additional safety data on the use of alogliptin in patients with renal impairment (in place of conducting the 2 separate renal safety studies which are currently pending review by the FDA)?

   FDA Pre-Meeting Response: Yes. Additional safety data on patients with renal impairment should be obtained in the form of a sub-study within this CV trial. This sub-study would need to enroll a sufficient number of patients with moderate and severe renal failure, with sufficient exposure time. The Sponsor is asked to provide an estimate of the number of patients with moderate and severe renal impairment that the Sponsor proposes to evaluate in such a substudy together with the estimated number of these patients who will be exposed to alogliptin and comparator for at least 1 year.

   The Sponsor's proposal to use the MDRD formula to estimate glomerular filtration rate (GFR) for inclusion criteria seems reasonable. However, it is recommended that the Sponsor use the standardized creatinine assay (refer Miller G. Am J Kidney Dis. 2008:645-

648). As supportive analyses, the Sponsor is asked to also present renal function, efficacy, and safety data using the Cockroft-Gault formula.

As stated above, the trial should include prespecified renal safety endpoints.

With regard to dose reductions for changes in renal function as measured by the MDRD formula after randomization: For the primary analysis of safety and tolerability endpoints, patients in the safety dataset should be analyzed in the renal severity subgroup in which they were randomized. For example, if a patient enters the study in the "moderate" renal status subgroup and then experiences a deterioration of renal function during the course of the study such that s/he progresses from "moderate" to "severe" renal impairment, this patient should still be included in the "moderate" status subgroup for purposes of the primary safety analysis. The rationale behind this request is to conduct the primary analysis in the same way that the randomization was established. If a substantial percentage of patients experience a change in severity status during the course of the study, the Sponsor should conduct a secondary analysis by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured.

Meeting Discussion: The Sponsor stated that at the time of the intermediate analysis, there will not be 1 year of exposure data for renal impairment patients. The Division stated that because there are no concerns with renal toxicity with alogliptin at this time, this is acceptable. Takeda's proposal estimates that 400-500 patients with moderate renal impairment will have 1 year of exposure to study medication and 80-100 patients with severe renal impairment will have 1 year of exposure to study medication. These numbers represent all exposure, not just alogliptin-exposed patients. The Division stated that the number of patients with moderate renal impairment is adequate. However, for exposure numbers for patients with severe renal impairment, the Division would look at what has been recommended to other sponsors and will provide a recommendation in the final meeting minutes.

Post-Meeting Comments: The Division requests that at least 100 patients with severe renal failure have at least one year of exposure to alogliptin.

Statistical Methods

8. Does the Agency agree with a single trial incorporating an adaptive Bayesian design to satisfy the Agency requirements to rule out excess CV risk greater than 1.3 and 1.8?

   FDA Pre-Meeting Response: The Division has the following requests for additional information concerning this proposed approach:

   A) A significant regulatory concern in this evaluation of cardiovascular risk is the actual coverage probability of the confidence bounds which are evaluated against the 1.8 and 1.3 non-inferiority margins. The Sponsor states (p. 56/74) "Simulation results will be used to establish the operating characteristics of this adaptive Bayesian design. In particular, the coverage probability of the 1-sided CIs, …, will be chosen to ensure an

overall false-rejection rate of at most 2.5% for the study and an appropriate level of power." This is a critical element of the proposed design. The Sponsor needs to provide more information about the proposed methods for ascertaining the operating characteristics of the adaptive Bayesian design.

B) An additional regulatory concern is raised by the proposed interim evaluations (b) (4) [redacted] The Division would like to ensure that the protocol for interim evaluations supports an unambiguous, traceable process. The Division requests additional information concerning this protocol.

Meeting Discussion: The Sponsor presented slides to provide additional information on the adaptive design. Bayesian methodology will serve as a monitoring tool. The final analysis will be based on traditional frequentist methods. The Division stated that it would be useful to have the references for the design. The Sponsor will provide the references and simulation program for review.

The Division asked whether there should be a minimum amount of exposure. The Sponsor said that this is possible, but stated that they would wait until receiving a recommendation from the Division regarding minimum exposure.

Post-Meeting Comments: As discussed in the Complete Response letter for the alogliptin NDA, you must provide controlled data for at least 500 patients with at least 1-year total exposure to alogliptin. These data can be derived from the cardiovascular safety trial and/or from other appropriate trials, such as the 1-year trial comparing alogliptin to titration of pioglitazone in patients on background metformin plus pioglitazone therapy and the 1-year trial comparing alogliptin to sulfonylurea in elderly patients.

After extensive discussions between FDA, (b) (4) [redacted] and the sponsor concerning the properties of the simulations, the sponsor proposed a different strategy for the analysis of accumulating CV events using a group sequential design. Biometrics has reviewed the proposed statistical analysis. Review comments will be forwarded to the sponsor.

9. Does the Agency agree with the statistical methods proposed for the interim analyses and for the final analysis?

FDA Pre-Meeting Response: Refer to the comments in response to Question 8.

Meeting Discussion: The Division stated that clinically important secondary endpoints not part of the primary composite endpoint should have type 1 error control.

TGRD Comment:
• Originally, in our Type A Briefing Document, TGRD proposed (b) (4) [redacted]

[redacted] (b) (4) However, during the Type A meeting, TGRD agreed to FDA's recommendation to use a more traditional MACE composite as the primary endpoint [redacted] (b) (4) and does not recall the Agency stating during our meeting that "clinically important secondary endpoints should have type 1 error control".

TGRD therefore believes that the statement under Meeting Discussion should be removed.

FDA Response to TGRD Comment: We wish to clarify the response under Meeting Discussion to read as follows: You should control type 1 error for the clinically important secondary endpoints that you would like the Division to consider for inclusion in labeling. Other comments on labeling are premature and will be deferred until after review of your submitted study results.

10. Does the Agency agree with the proposed statistical assumptions for this study?

    FDA Pre-Meeting Response: The statistical assumptions used in calculating the size of the study were constant proportional hazards, exponential survival curves and a non-adaptive design, 90% power with respect to a non-inferiority margin of 1.3, true HR of 1.1, one-sided 0.025 level of significance. These assumptions are reasonable from the statistical perspective. Additional assumptions were a placebo MACE composite rate of 3.5% annually, accrual time of 2 years, maximum length of follow-up of 4.5 years, and loss of follow-up of 1% annually. Note the MACE composite event rate will depend on the types of events included in the composite. The Sponsor is asked to provide justification for these assumptions.

    Meeting Discussion: None

11. Takeda currently does not plan to conduct a meta-analysis combining this study with any other previously completed controlled studies. Does the Agency agree that this study can stand-alone to satisfy the guidance criteria for both the interim analysis and the primary analysis?

    FDA Pre-Meeting Response: Yes, the Division agrees that this study should stand alone for assessing cardiovascular safety.

    Meeting Discussion: None

    TGRD Comment:
    • For completeness, TGRD would like the Division to add a Post-Meeting Comment to capture agreements reached during the July 10, 2009 teleconference. TGRD suggests the following:

(b) (4)

FDA Response to TGRD Comment*: We do not concur with your suggestion. As mentioned in our Post-Meeting comments, the Division will consider the results from the dedicated cardiovascular trial as primary when assessing whether the 1.8 criterion has been met. Results from a pooled analysis across all controlled data will be considered supportive because most of the trials that will be included in this pooled analysis were not rigorously designed to assess cardiovascular risk (e.g., no blinded, prospective adjudication, lack of prespecified cardiovascular endpoints of interest, etc.). A statistical analysis plan should be submitted for the meta-analysis.

Long-Term Exposure

12. Does the Agency find this acceptable to support the long-term safety of alogliptin?

    FDA Pre-Meeting Response: Although the final decision remains a review issue, this study should be adequate to support the long-term safety of alogliptin, provided it incorporates the listed comments.

    Meeting Discussion: None

Regulatory

13. If the Agency determines Takeda must collect additional data to satisfy the 1.8 criterion prior to approval, does the Agency agree that the proposed submission contents as outlined above would be adequate for the Agency to determine the approvability of alogliptin?

    FDA Pre-Meeting Response: Although the final decision remains a review issue, this study should be adequate to determine the approvability of alogliptin from a cardiovascular safety standpoint, provided the study incorporates the listed comments. The current protocol may need to be amended or other studies may be needed if safety issues are identified in the alogliptin NDA that is currently under review.

    Meeting Discussion: None

    TGRD Comment:
    • Since additional discussions regarding the CV outcomes study occurred following the PDUFA date of the alogliptin NDA, TGRD suggests, for completeness, that the following be added as a Post-Meeting Comment:

(b) (4)

***FDA Response to TGRD Comment*: We add the following Post-Meeting Comment:**

"Post-Meeting Comment: The final action taken and the list of deficiencies identified based on review of the alogliptin NDA were described in the Complete Response letter issued on June 26, 2009."

14. If these data are submitted to address a complete response letter, Takeda anticipates that these data would be subject to a 6-month review cycle. Is Takeda's understanding correct? Additionally, does the Agency agree that this focused data package could undergo an expedited review cycle of less than 6 months?

    FDA Pre-Meeting Response: A submission to address a complete response letter is subject to a 6-month review cycle regardless of the amount of data included in the submission. Therefore, the Sponsor should anticipate a 6-month review cycle if these data are submitted to address a complete response letter. Clinical reviews of the alogliptin NDA are still ongoing; therefore, a final action and a complete list of deficiencies (if applicable) have not been determined.

    Meeting Discussion: None

    TGRD Comment:
    • Since additional discussions regarding the CV outcomes study occurred following the PDUFA date of the alogliptin NDA, TGRD suggests, for completeness, that the following be added as a *Post-Meeting Comment*:

    [redacted] (b) (4)

    ***FDA Response to TGRD Comment*: We add the following Post-Meeting Comment:**

    "Post-Meeting Comment: The final action taken and the list of deficiencies identified based on review of the alogliptin NDA were described in the Complete Response letter issued on June 26, 2009."

15. If the results of the interim analysis show that the upper bound of the confidence interval for the estimated risk ratio is less than 1.8, Takeda would expect (1) alogliptin to be approved for general use in patients with T2DM, and (2) that a statement be included in the product labeling such as, [redacted] (b) (4) Does the Agency agree?

    FDA Pre-Meeting Response: Clinical reviews of the alogliptin NDA are still ongoing; therefore, a decision on approvability and, if applicable, a list of deficiencies have not been

determined. Antidiabetic drugs that meet the 1.8 or 1.3 criteria would likely have standard language about cardiovascular safety in the package insert but the exact wording has not yet been decided upon. (b) (4) (b) (4)

Meeting Discussion: The Sponsor asked whether alogliptin would be approved for general use in patients with type 2 diabetes if the proposed study is conducted with revisions agreed to by FDA. The Division stated that the label would have the general type 2 diabetes indication. The population studied would be detailed in the Clinical Studies section.

16. If the final analysis satisfies a non-inferiority margin of 1.3, Takeda would expect a labeling statement such as, (b) (4) Does the Agency agree?

FDA Pre-Meeting Response: Refer to the response to Question 15.

Meeting Discussion: None

17. It is Takeda's expectation that the current proposed study will rule out excess CV risk with alogliptin. Coupled with the knowledge that pioglitazone does not increase CV risk, can Takeda anticipate that a separate CV safety study will not be required for marketing approval of the alogliptin/pioglitazone fixed-dose combination (FDC) product? Also, if Takeda must collect additional data to satisfy the 1.8 criterion with alogliptin prior to approval, and assuming adequacy of the interim analysis, can Takeda expect a concurrent action on the alogliptin (NDA 22-271) and FDC (NDA 22-426) applications?

FDA Pre-Meeting Response: Clinical reviews of the alogliptin + pioglitazone NDA are still ongoing. Therefore, a decision on approvability and, if applicable, a list of deficiencies have not been determined. If individual components of a FDC product do not increase CV risk, then the FDC product will not likely need a separate dedicated CV safety trial provided there is no pharmacological basis for a detrimental interaction between the two components on CV safety. However, the Sponsor should include a reasonable number of patients on background pioglitazone therapy in the planned CV trial. The Sponsor is asked to provide an estimate of the number of alogliptin and comparator-treated patients the Sponsor proposes to enroll who will be on background pioglitazone therapy. A similar comment applies if the Sponsor develops a FDC tablet of alogliptin and metformin.

Meeting Discussion: The Sponsor stated that 10-20% of the patients (~300) will be on background pioglitazone therapy at the time of randomization and that approximately 80% of the patients would be on background metformin therapy at the time of randomization.

<u>TGRD Comment</u>:
During the Type A meeting, the Agency agreed that a separate CV study with the alogliptin/pioglitazone FDC would not be required based on: (1) data from PROactive demonstrating no increase in CV risk with pioglitazone use, and (2) no evidence of an interaction between the two components (based on results from alogliptin/pioglitazone phase 3 program). The Agency also agreed that a separate CV study with alogliptin/metformin FDC would also not be needed based on (1) metformin showing no association with an increase in CV risk, and (2) the proposed CV outcomes study with alogliptin is expected to include at least 80% of subjects on metformin.

For completeness, TGRD suggests the following revisions under Meeting Discussion:

"Meeting Discussion: The Sponsor stated that 10-20% of the patients (~300) will be on background pioglitazone therapy at the time of randomization. The Agency agreed that based on prior data on CV safety with pioglitazone, and assuming no evidence of any interaction between the two components on CV safety, a separate CV study with the alogliptin/pioglitazone FDC would not be required.

The Sponsor also stated that approximately 80% of the patients would be on background metformin therapy at the time of randomization, to which the Division also agreed that a separate CV study with the alogliptin/metformin FDC would not be required, provided there is no interaction between the two components on CV safety."

<u>FDA Response to TGRD Comment</u>: Yes, we agree.

Additional Comments

1. In Appendix D, the Sponsor is asked to specially mention the Food and Drug Administration.

   <u>Meeting Discussion</u>: None

2. The Sponsor should clarify the cardiac biomarkers to be obtained to establish whether or not a patient has a myocardial infarction (CPK, CPK-MB, Troponin I or T). Also, the Sponsor should clarify whether or not these biomarkers will be measured locally, centrally, or both and the timing of when these cardiac biomarkers will be obtained.

   <u>Meeting Discussion</u>: None

   <u>TGRD Comment</u>:

   • TGRD provided clarification to this comment during the Type A meeting. TGRD suggests the following be added under Meeting Discussion:

"Meeting Discussion: The Sponsor stated that these cardiac biomarkers will be measured locally at the time of the event and these data would be collected and used for adjudication by the CEC."

FDA Response to TGRD Comment: ***Yes, we agree.***

3. Appendix E, Inclusion Criteria Definition for Acute Coronary Syndromes
   a. Myocardial Infarction (MI)
      The Division recommends using Thygesen's "Universal Definition of Myocardial Infarction" with one minor modification for periprocedural MI (the Agency is currently working on developing a better definition for periprocedural MI)

   b. Unstable Angina Requiring Hospitalization
      - The Sponsor should refer to the ACC/AHA 2007 Guidelines for the Management of Patient with Unstable Angina/Non ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the definition of unstable angina.

      - The Sponsor propose using the term "unstable angina" when hospitalization is required to treat one or more episodes of ischemic discomfort at rest lasting (b) (4) minutes and supported by the ECG criteria further discussed in Bullet #3 below. Since the Division is currently in the process of attempting to standardize definitions and duration of symptoms, at this time, the Division recommends modifying this definition from (b) (4) minutes to ≥ 10 minutes within 24 hours prior to hospitalization. At the time of the formal protocol submission, the Division reserves the right to recommend additional modifications to these and other definitions as the Division attempts to finalize these definitions.

      - Instead of using the proposed ECG criteria (b) (4) the Sponsor should use the criteria as specified by Thygesen below for myocardial ischemia:

Table 3 ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)

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Table 4 ECG changes associated with prior myocardial infarction

COPYRIGHT MATERIAL

Thygesen, Kristian, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction, Circulation. 2007; 6-7.

Meeting Discussion: The Division clarified that these definitions are for diagnosis and not for use as inclusion criteria.

4. In the demographic information for the trial, the Sponsor should obtain a present, past, or ongoing history of cancer, date of diagnosis, date(s) and types of treatment, cancer site, and histopathology results, if possible.

   Meeting Discussion: None

5. Although the Sponsor should conduct standard safety analyses for the renal substudy, the Sponsor could consider only analyzing serious adverse events, adverse events causing study drug discontinuation, and pre-defined adverse events of interest for the larger CV trial.

   Meeting Discussion: None

6. It is acceptable to not subject the components of the primary composite endpoint to expedited reporting to FDA.
   Meeting Discussion: None

7. The protocol should contain the specific details on standards of care that investigators should follow for glycemic control and for control of cardiovascular risk factors.

   Meeting Discussion: None

   TGRD Comment:
   • TGRD suggests the following for completeness under Meeting Discussion:

   Meeting Discussion: Refer to the response to Question 1

   FDA Response to TGRD Comment: Yes, we agree.

Your submission dated August 31, 2009, also requested a response to the question below, to which we provide a response.

TGRD Question:
In addition, TGRD would like to request, as a reference for development of future diabetes compounds, a better understanding of the reason that the Agency does not believe that hospitalization due to unstable angina is *equally weighted* to CV death, non-fatal MI and non-fatal stroke. Specifically, is it because an adequate (and sufficiently objective) adjudication criteria has not been defined or is it a fundamental belief that the underlying pathophysiology of unstable angina is not equivalent to an acute event of myocardial infarction?

<u>FDA Response to TGRD Question</u>: There are at least two concerns with an endpoint of hospitalization for unstable angina. First, as previously noted, the definition of hospitalization for unstable angina has been problematic. Because unstable angina comprises 40% of acute coronary syndrome events, it is critical to ensure that such an endpoint is rigorously defined, especially in the setting of a non-inferiority trial. In addition, it is questionable whether the morbidity and mortality associated with hospitalization for unstable angina is comparable to that associated with cardiovascular death or the processes of acute myocardial infarction or stroke, which cause irreversible injury. For this reason, if the findings with hospitalization for unstable angina trend favorably but the findings with the more traditional endpoints trend unfavorably for alogliptin, the Division will question whether cardiovascular safety has been demonstrated even if the overall composite endpoint meets the 1.8 criterion.

If you have any questions, please contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22271	GI-1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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
10/26/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-271

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

We also refer to the meeting between representatives of your firm and the FDA held on April 27, 2009. The purpose of the meeting was to discuss your proposed cardiovascular outcomes trial.

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) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from meeting held on April 27, 2009

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 27, 2009
TIME: 3:00 – 4:00 P.M.
LOCATION: White Oak Campus, Silver Spring, MD
APPLICATION: NDA 22-271
DRUG NAME: Nesina (alogliptin) Tablets
TYPE OF MEETING: Type A

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES:

Office of Drug Evaluation II

Curtis Rosebraugh, MD	Director

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, MD	Director
Amy Egan, MD	Deputy Director for Safety
Hylton Joffe, MD, MMSc	Clinical Team Leader, Diabetes Team I
Ilan Irony, MD	Acting Clinical Team Leader, Diabetes Team II
Valerie Pratt, MD	Clinical Reviewer
Karen Hicks, MD	Clinical Reviewer
Lina AlJuburi, PharmD, MS	Chief, Project Management Staff
Julie Marchick, MPH	Regulatory Project Manager

Office of Biostatistics

J. Todd Sahlroot, PhD	Deputy Division Director
Janice Derr, PhD	Reviewer
David Hoberman, PhD	Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Takeda Global Research & Development Center

Penny Fleck, MT	Director, Clinical Science
Thomas Strack, MD	Vice President, Clinical Science
Neila Smith, MD	Senior Medical Director, Pharmacovigilance
Craig Wilson, PhD	Principal Statistician, Biostatistics
Vipin Arora, PhD	Associate Director, Biostatistics
Yukari Nishikata	Senior Director, Takeda Japan Liaison
Mick Roebel, PhD	Senior Director, Regulatory Affairs
Mary Mantock	Senior Director, Regulatory Affairs (Europe)
Christie Idemoto, MS	Manager, Regulatory Affairs

External Consultants

(b) (4)

BACKGROUND:

On September 17, 2004, Takeda Global Research & Development (TGRD) submitted IND 69,707 for SYR-322 (alogliptin) tablets, a dipeptidyl-peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. On December 27, 2007, TGRD submitted NDA 22-271 for alogliptin.

The Agency issued *Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* in December 2008.

MEETING OBJECTIVES:

To discuss the Sponsor's proposed cardiovascular outcomes trial.

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 April 24, 2009, follow in bold. A summary of the meeting discussion is italicized. Post-meeting comments are italicized and underlined.

Protocol Design

1. Does the Agency agree that the protocol is appropriately designed to assess the CV risk associated with alogliptin?

   Response: The Division provides preliminary comments below. Additional comments may be forthcoming after the Division has reviewed the updated, complete protocol (which should include definitions for all endpoints of interest and the adjudication committee charter).

   While the Division recognizes that the December 2008 *Guidance to Industry Diabetes Mellitus – Evaluating CV Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes Mellitus* discusses the possibility of including CV events other than CV death, MI, and stroke, the Division encourages a more traditional MACE composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. The Division recommends a more traditional MACE endpoint (b) (4) **Should the Sponsor proceed with the proposed composite endpoint, the contribution of each component of the composite endpoint to the overall efficacy findings will be a consideration to whether the Sponsor has ruled out an unacceptable cardiovascular risk associated with alogliptin.**

   With respect to stroke, the Division recommends classifying the event as ischemic (non-hemorrhagic), hemorrhagic, or unknown, and the Division recommends classifying stroke severity according to the modified Rankin Scale.

   Furthermore, the Division recommends examining hospitalization for unstable angina (with or without urgent revascularization), hospitalization for congestive heart failure, all cause mortality, stent thrombosis, hospitalization for other cardiovascular causes, and lower extremity amputation, primarily due to ischemia, as secondary endpoints in

addition to the secondary endpoints the Sponsor has already proposed of CV death, nonfatal MI, and nonfatal stroke. Hospitalization for other cardiovascular causes would include pulmonary embolism, ruptured aortic aneurysm, and arrhythmia (specifically, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, torsade de pointes, second degree heart block type 2, third degree heart block, and symptomatic bradycardia requiring pacemaker placement).

Meeting Discussion: The Sponsor agreed with the recommendation (b) (4)

The Sponsor said that it may not be feasible to classify stroke severity on the Rankin Scale because there may not be enough information in the inpatient records. However, the Sponsor will take the recommendation under advisement.

The Division stated that the Agency is in the process of standardizing the definitions for cardiovascular endpoints. The recommendations included in the preliminary responses represented the Division's thinking at the time of the meeting (please see the Post-Meeting Comment below for updated recommendations).

The Sponsor presented a slide (see attached slide #3) of the proposed secondary endpoints. It is acceptable for the Sponsor to analyze various composites of cardiovascular endpoints as secondary endpoints; however, the Division stated that the Sponsor should also evaluate the cardiovascular endpoints individually as secondary endpoints.

The Sponsor stated that investigators will be encouraged to manage patients based on regional guidelines. The Sponsor plans to submit to the Division a document with regional guidance, which will be separate from the protocol. The Sponsor will document that investigators are trained based on the regional guidance and any changes to the regional guidance will be tracked by the Sponsor. The Division stated that this is acceptable.

The Sponsor will provide the adjudication charter for review.

Post-Meeting Comment: The Division is further along in the process of standardizing recommendations and definitions for cardiovascular endpoints for use by all sponsors who are developing treatments for type 2 diabetes. See the attached appendices for the most recent version of these documents. Note that the cardiovascular endpoint definitions have not been finalized. Pharmaceutical Research and Manufacturers of America (PhRMA) is in the process of testing the workability of these definitions. Based on the results of this testing, additional modifications may be forthcoming.

The Division acknowledges subsequent discussions with the Sponsor regarding the design of the cardiovascular trial since this Type A meeting, including discussions related to the inclusion criteria (see Post-Meeting Comment under Question 2), the primary endpoint, and the statistical analysis plan. In subsequent telephone conferences on June 3, 2009 and July 10, 2009, the sponsor proposed (b) (4) (b) (4)

Therefore, the Division recommended that the primary endpoint include cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke only (b) (4) *Should the Sponsor proceed with*

a primary composite endpoint (b) (4) *the contribution of this component of the composite endpoint to the overall findings would be a consideration as to whether the Sponsor had ruled out unacceptable cardiovascular risk with alogliptin. The Division acknowledges the sponsor's recent submission of the amended clinical protocol for the cardiovascular trial. Additional comments may be forthcoming after our review is completed.*

2. Does the Agency agree that the higher risk T2DM population chosen for this study is appropriate?

   Response: Yes, the Division agrees that the higher risk type 2 diabetes population chosen for this study is appropriate. However, (b) (4) **the Division recommends randomizing patients with a diagnosis of ACS 2-4 weeks after the index ACS event, because many cardiovascular endpoints in this population occur early.**

   Meeting Discussion: The Sponsor proposed randomizing patients 15 to 60 days following a diagnosis of ACS. This would allow the physician to stabilize the patient and still be able to randomize the patient. The Division stated that the Sponsor's proposal is reasonable.

   The Sponsor presented a slide (see attached slide #4) with the justification for a revised sample size. The post-ACS event rate was re-estimated at 6% because of the changed criterion. The Division stated that this seems reasonable.

   Post-Meeting Comment: Since the Meeting on April 27, 2009, there has been further internal discussion within FDA about cardiovascular trial designs for treatments developed for diabetes. At a meeting between members of the Division of Cardio-Renal Products and the Division of Metabolism and Endocrinology Products on May 11, 2009, the general concensus was not to enroll patients with ACS prior to 2 months from the index event because all of the early events could add noise to the overall trial and bias towards showing non-inferiority.

   As a result, in a telephone conference with the sponsor on June 3, 2009, we recommended enrolling patients with ACS at least 2 months after the index event, which would likely change the sample size and trial duration. In addition to enrolling patients with ACS and renal insufficiency, we recommended enriching the trial with patients having other high risk characteristics too, in order to make the result of the cardiovascular outcomes trial more generalizable.

   Despite these potential limitations, the sponsor still wishes to keep the inclusion criterion as 15-60 days following a diagnosis of ACS. The Division of Metabolism and Endocrinology Products stated this will be acceptable; however, if there are many early events, the adequacy of the findings will be a review issue.

Study Endpoints

3. Does the Agency agree with the proposed primary endpoint of time from randomization to the first occurrence of any of the events in the primary MACE composite of CV death,

nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina (with or without urgent revascularization)?

Response: Refer to the response to Question 1.

Meeting Discussion: None

4. Does the Agency agree that the secondary endpoint adequately supports the primary endpoint?

   Response: Refer to the response to Question 1.

   Meeting Discussion: None

General Safety Evaluation

5. Does the Agency agree with the safety data that Takeda plans to collect and analyze in the proposed CV outcomes study?

   Response: No, the Division does not agree. Although targeted questions can be used to capture adverse events (AEs), the Division recommends that investigators use check boxes to query patients and to report cardiovascular adverse events of interest. This event reporting will trigger review by the Clinical Events Committee (CEC). Emergency Room, hospital, and revascularization (percutaneous coronary intervention, coronary artery bypass grafting, peripheral) reports and amputation operative reports, 12-lead electrocardiograms (ECGs), and laboratory results will need to be obtained for review by the CEC for the endpoints described in Question 1 contributing to the primary and secondary endpoints.

   Additionally, if a patient is hospitalized for acute coronary syndrome or revascularization procedures after randomization, serial cardiac enzymes (creatine phosphokinase [CPK], CK-MB, troponin) and 12-lead ECGs should be obtained per protocol.

   Furthermore, it is essential that investigator "verbatim terms" be recorded and listed in the adverse events dataset submitted to the Agency with the Clinical Study Report, along with lower level terms, preferred terms, and system organ classes (SOCs) to which the verbatim term was originally coded. If there are any changes made to the verbatim terms, these changes must be documented as well as the reason for the changes, and this information should be submitted with the Clinical Study Report.

   With the Clinical Study Report, the Division recommends that 5 patient listings be submitted:

   - **Listing of all investigator reported events**
   - **Listing of all CEC adjudicated events**
   - **Listing of all investigator reported events that were also adjudicated by the CEC to be events**
   - **Listing of all investigator reported events that were downgraded as "non events" by the CEC**

- **Listing of CEC adjudicated events that were not thought to be events by the investigator and were not reported by the investigator**

Women of childbearing potential should be educated to contact the investigator for a possible pregnancy test if changes in menstrual bleeding are observed.

The Sponsor should follow adverse events of angioedema and pancreatitis as events of special interest.

The trial should include prespecified renal safety endpoints.

Meeting Discussion: The Sponsor presented a slide (see attached slide #9) listing the adverse events to be collected. The Sponsor stated that all hospitalizations would be considered serious adverse events. The Sponsor will not use general open-ended questions to collect adverse events. The Division recommended using check-boxes for cardiovascular events, including revascularization procedures. The Sponsor stated that the check-boxes will serve as a trigger for investigators to complete case report forms for additional data.

The Division asked that the Sponsor include a list of renal safety endpoints in the protocol. The Sponsor presented a slide (see attached slide #10), listing the proposed renal safety endpoints. The Division agreed to provide comments on the renal endpoints after review of the full protocol. The Division asked whether the Sponsor will assess hepatotoxicity. The Sponsor stated that the trial will include routine measurements of liver tests and will include stopping criteria based on liver test abnormalities.

Dose Selection

6. Does the Agency agree with the proposed dose selection for this study?

   Response: Consider dose adjustment to 12.5 mg for patients with mild renal impairment due to a mean exposure increase of 69% in this patient population.

   Meeting Discussion: None

Evaluation of Subjects with Renal Impairment

7. Does the Agency agree that the proposed CV outcomes study can be used to provide additional safety data on the use of alogliptin in patients with renal impairment (in place of conducting the 2 separate renal safety studies which are currently pending review by the FDA)?

   Response: Yes. Additional safety data on patients with renal impairment should be obtained in the form of a sub-study within this CV trial. This sub-study would need to enroll a sufficient number of patients with moderate and severe renal failure, with sufficient exposure time. The Sponsor is asked to provide an estimate of the number of patients with moderate and severe renal impairment that the Sponsor proposes to evaluate in such a substudy together with the estimated number of these patients who will be exposed to alogliptin and comparator for at least 1 year.

The Sponsor's proposal to use the MDRD formula to estimate glomerular filtration rate (GFR) for inclusion criteria seems reasonable. However, it is recommended that the Sponsor use the standardized creatinine assay (refer Miller G. Am J Kidney Dis. 2008:645-648). As supportive analyses, the Sponsor is asked to also present renal function, efficacy, and safety data using the Cockroft-Gault formula.

As stated above, the trial should include prespecified renal safety endpoints.

With regard to dose reductions for changes in renal function as measured by the MDRD formula after randomization: For the primary analysis of safety and tolerability endpoints, patients in the safety dataset should be analyzed in the renal severity subgroup in which they were randomized. For example, if a patient enters the study in the "moderate" renal status subgroup and then experiences a deterioration of renal function during the course of the study such that s/he progresses from "moderate" to "severe" renal impairment, this patient should still be included in the "moderate" status subgroup for purposes of the primary safety analysis. The rationale behind this request is to conduct the primary analysis in the same way that the randomization was established. If a substantial percentage of patients experience a change in severity status during the course of the study, the Sponsor should conduct a secondary analysis by renal severity subgroup according to the actual severity status of patients at the time period in which the study endpoint is measured.

Meeting Discussion: The Sponsor stated that at the time of the intermediate analysis, there will not be 1 year of exposure data for renal impairment patients. The Division stated that because there are no concerns with renal toxicity with alogliptin at this time, this is acceptable. Takeda's proposal estimates that 400-500 patients with moderate renal impairment will have 1 year of exposure to study medication and 80-100 patients with severe renal impairment will have 1 year of exposure to study medication. These numbers represent all exposure, not just alogliptin-exposed patients. The Division stated that the number of patients with moderate renal impairment is adequate. However, for exposure numbers for patients with severe renal impairment, the Division would look at what has been recommended to other sponsors and will provide a recommendation in the final meeting minutes.

Post Meeting Comments: The Division requests that at least 100 patients with severe renal failure have at least one year of exposure to alogliptin.

Statistical Methods

8. Does the Agency agree with a single trial incorporating an adaptive Bayesian design to satisfy the Agency requirements to rule out excess CV risk greater than 1.3 and 1.8?

   Response: The Division has the following requests for additional information concerning this proposed approach:

   A) A significant regulatory concern in this evaluation of cardiovascular risk is the actual coverage probability of the confidence bounds which are evaluated against the 1.8 and 1.3 non-inferiority margins. The Sponsor states (p. 56/74) "Simulation results will be used to establish the operating characteristics of this adaptive Bayesian design. In particular, the coverage probability of the 1-sided

CIs, …, will be chosen to ensure an overall false-rejection rate of at most 2.5% for the study and an appropriate level of power." This is a critical element of the proposed design. The Sponsor needs to provide more information about the proposed methods for ascertaining the operating characteristics of the adaptive Bayesian design.

B) An additional regulatory concern is raised by the proposed interim evaluations (b) (4) **The Division would like to ensure that the protocol for interim evaluations supports an unambiguous, traceable process. The Division requests additional information concerning this protocol.**

Meeting Discussion: The Sponsor presented slides to provide additional information on the adaptive design. Bayesian methodology will serve as a monitoring tool. The final analysis will be based on traditional frequentist methods. The Division stated that it would be useful to have the references for the design. The Sponsor will provide the references and simulation program for review.

The Division asked whether there should be a minimum amount of exposure. The Sponsor said that this is possible, but stated that they would wait until receiving a recommendation from the Division regarding minimum exposure.

Post-Meeting Comments: As discussed in the Complete Response letter for the alogliptin NDA, you must provide controlled data for at least 500 patients with at least 1-year total exposure to alogliptin. These data can be derived from the cardiovascular safety trial and/or from other appropriate trials, such as the 1-year trial comparing alogliptin to titration of pioglitazone in patients on background metformin plus pioglitazone therapy and the 1-year trial comparing alogliptin to sulfonylurea in elderly patients.

After extensive discussions between FDA, (b) (4) *and the sponsor concerning the properties of the simulations, the sponsor proposed a different strategy for the analysis of accumulating CV events using a group sequential design. Biometrics has reviewed the proposed statistical analysis. Review comments will be forwarded to the sponsor.*

9. Does the Agency agree with the statistical methods proposed for the interim analyses and for the final analysis?

Response: Refer to the comments in response to Question 8.

Meeting Discussion: The Division stated that clinically important secondary endpoints not part of the primary composite endpoint should have type 1 error control.

10. Does the Agency agree with the proposed statistical assumptions for this study?

Response: The statistical assumptions used in calculating the size of the study were constant proportional hazards, exponential survival curves and a non-adaptive design, 90% power with respect to a non-inferiority margin of 1.3, true HR of 1.1, one-sided 0.025 level of significance. These assumptions are reasonable from the statistical perspective. Additional assumptions were a placebo MACE composite rate of 3.5%

annually, accrual time of 2 years, maximum length of follow-up of 4.5 years, and loss of follow-up of 1% annually. Note the MACE composite event rate will depend on the types of events included in the composite. The Sponsor is asked to provide justification for these assumptions.

Meeting Discussion: None

11. Takeda currently does not plan to conduct a meta-analysis combining this study with any other previously completed controlled studies. Does the Agency agree that this study can stand-alone to satisfy the guidance criteria for both the interim analysis and the primary analysis?

    Response: Yes, the Division agrees that this study should stand alone for assessing cardiovascular safety.

    Meeting Discussion: None

Long-Term Exposure

12. Does the Agency find this acceptable to support the long-term safety of alogliptin?

    Response: Although the final decision remains a review issue, this study should be adequate to support the long-term safety of alogliptin, provided it incorporates the listed comments.

    Meeting Discussion: None

Regulatory

13. If the Agency determines Takeda must collect additional data to satisfy the 1.8 criterion prior to approval, does the Agency agree that the proposed submission contents as outlined above would be adequate for the Agency to determine the approvability of alogliptin?

    Response: Although the final decision remains a review issue, this study should be adequate to determine the approvability of alogliptin from a cardiovascular safety standpoint, provided the study incorporates the listed comments. The current protocol may need to be amended or other studies may be needed if safety issues are identified in the alogliptin NDA that is currently under review.

    Meeting Discussion: None

14. If these data are submitted to address a complete response letter, Takeda anticipates that these data would be subject to a 6-month review cycle. Is Takeda's understanding correct? Additionally, does the Agency agree that this focused data package could undergo an expedited review cycle of less than 6 months?

    Response: A submission to address a complete response letter is subject to a 6-month review cycle regardless of the amount of data included in the submission. Therefore, the Sponsor should anticipate a 6-month review cycle if these data are submitted to address a complete response letter. Clinical reviews of the alogliptin NDA are still

ongoing; therefore, a final action and a complete list of deficiencies (if applicable) have not been determined.

Meeting Discussion: None

15. If the results of the interim analysis show that the upper bound of the confidence interval for the estimated risk ratio is less than 1.8, Takeda would expect (1) alogliptin to be approved for general use in patients with T2DM, and (2) that a statement be included in the product labeling such as, (b) (4) Does the Agency agree?

    Response: Clinical reviews of the alogliptin NDA are still ongoing; therefore, a decision on approvability and, if applicable, a list of deficiencies have not been determined. Antidiabetic drugs that meet the 1.8 or 1.3 criteria would likely have standard language about cardiovascular safety in the package insert but the exact wording has not yet been decided upon. (b) (4) (b) (4)

    Meeting Discussion: The Sponsor asked whether alogliptin would be approved for general use in patients with type 2 diabetes if the proposed study is conducted with revisions agreed to by FDA. The Division stated that the label would have the general type 2 diabetes indication. The population studied would be detailed in the Clinical Studies section.

16. If the final analysis satisfies a non-inferiority margin of 1.3, Takeda would expect a labeling statement such as, (b) (4) Does the Agency agree?

    Response: Refer to the response to Question 15.

    Meeting Discussion: None

17. It is Takeda's expectation that the current proposed study will rule out excess CV risk with alogliptin. Coupled with the knowledge that pioglitazone does not increase CV risk, can Takeda anticipate that a separate CV safety study will not be required for marketing approval of the alogliptin/pioglitazone fixed-dose combination (FDC) product? Also, if Takeda must collect additional data to satisfy the 1.8 criterion with alogliptin prior to approval, and assuming adequacy of the interim analysis, can Takeda expect a concurrent action on the alogliptin (NDA 22-271) and FDC (NDA 22-426) applications?

    Response: Clinical reviews of the alogliptin + pioglitazone NDA are still ongoing. Therefore, a decision on approvability and, if applicable, a list of deficiencies have not been determined. If individual components of a FDC product do not increase CV risk, then the FDC product will not likely need a separate dedicated CV safety trial provided there is no pharmacological basis for a detrimental interaction between the two components on CV safety. However, the Sponsor should include a reasonable number of patients on background pioglitazone therapy in the planned CV trial. The

Sponsor is asked to provide an estimate of the number of alogliptin and comparator-treated patients the Sponsor proposes to enroll who will be on background pioglitazone therapy. A similar comment applies if the Sponsor develops a FDC tablet of alogliptin and metformin.

Meeting Discussion: The Sponsor stated that 10-20% of the patients (~300) will be on background pioglitazone therapy at the time of randomization and that approximately 80% of the patients would be on background metformin therapy at the time of randomization.

Additional Comments

1. **In Appendix D, the Sponsor is asked to specially mention the Food and Drug Administration.**

   Meeting Discussion: None

2. **The Sponsor should clarify the cardiac biomarkers to be obtained to establish whether or not a patient has a myocardial infarction (CPK, CPK-MB, Troponin I or T). Also, the Sponsor should clarify whether or not these biomarkers will be measured locally, centrally, or both and the timing of when these cardiac biomarkers will be obtained.**

   Meeting Discussion: None

3. **Appendix E, Inclusion Criteria Definition for Acute Coronary Syndromes**
   a. **Myocardial Infarction (MI)**
      The Division recommends using Thygesen's "Universal Definition of Myocardial Infarction" with one minor modification for periprocedural MI (the Agency is currently working on developing a better definition for periprocedural MI)

   b. **Unstable Angina Requiring Hospitalization**
      - **The Sponsor should refer to the ACC/AHA 2007 Guidelines for the Management of Patient with Unstable Angina/Non ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines for the definition of unstable angina.**

      - **The Sponsor propose using the term "unstable angina" when hospitalization is required to treat one or more episodes of ischemic discomfort at rest lasting** (b) (4) **minutes and supported by the ECG criteria further discussed in Bullet #3 below. Since the Division is currently in the process of attempting to standardize definitions and duration of symptoms, at this time, the Division recommends modifying this definition from** (b) (4) **minutes to ≥ 10 minutes within 24 hours prior to hospitalization. At the time of the formal protocol submission, the Division reserves the right to recommend additional modifications to these and other definitions as the Division attempts to finalize these definitions.**

      - **Instead of using the proposed ECG criteria** (b) (4) **, the Sponsor should use the criteria as specified by Thygesen below for myocardial ischemia:**

Table 3 ECG manifestations of acute myocardial ischaemia (in absence of LVH and LBBB)

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Table 4 ECG changes associated with prior myocardial infarction

COPYRIGHT MATERIAL

Thygesen, Kristian, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal Definition of Myocardial Infarction, Circulation. 2007; 6-7.

Meeting Discussion: The Division clarified that these definitions are for diagnosis and not for use as inclusion criteria.

4. **In the demographic information for the trial, the Sponsor should obtain a present, past, or ongoing history of cancer, date of diagnosis, date(s) and types of treatment, cancer site, and histopathology results, if possible.**

   Meeting Discussion: None

5. **Although the Sponsor should conduct standard safety analyses for the renal substudy, the Sponsor could consider only analyzing serious adverse events, adverse events causing study drug discontinuation, and pre-defined adverse events of interest for the larger CV trial.**

   Meeting Discussion: None

6. **It is acceptable to not subject the components of the primary composite endpoint to expedited reporting to FDA.**
   Meeting Discussion: None

7. **The protocol should contain the specific details on standards of care that investigators should follow for glycemic control and for control of cardiovascular risk factors.**

   Meeting Discussion: None

ATTACHMENTS:

- Slides presented by Sponsor during the meeting
- Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations
- Endpoints and Standardized Data Collection for Cardiovascular Outcomes Trials: Draft Recommendations

Minutes Preparer: Julie Marchick
Chair Concurrence: Mary Parks

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b4 (CCI/TS) immediately following this page

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22271	GI 1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS
NDA 22271	GI 1	TAKEDA GLOBAL RESEARCH DEVELOPMENT CENTER INC	NESINA TABLETS

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/s/

JULIE C MARCHICK
08/26/2009

From: Joffe, Hylton
Sent: Friday, June 19, 2009 12:20 PM
To: Pratt, Valerie; Ripper, Leah W
Subject: Review of response to IR ltr on DSI inspection of the pivotal BE study

The sponsor confirmed that only those 2 subjects had adverse events documented on the source document but not on the case report form. The other adverse events had been appropriately put on the case report form in the original submission. Valerie is correct that the AE data are very limited in that study -- limited dosing and the doses did not exceed the doses for which they are seeking marketing.

Hope that helps.

Hylton

From: Pratt, Valerie
Sent: Thursday, June 18, 2009 1:59 PM
To: Ripper, Leah W; Joffe, Hylton
Subject: RE: Your review of NDA 22-271, alogliptin and the DSI inspection of the pivotal BE study

6/198/09

Dear Leah,

Honestly, study SYR-0322-027 was an open label, randomized, 2-period crossover, bioequivalence, *2 day* study in 72 healthy subjects. I therefore did not review it or its Aes in my NDA.

Valerie

From: Ripper, Leah W
Sent: Thursday, June 18, 2009 1:25 PM
To: Pratt, Valerie; Joffe, Hylton
Subject: FW: Your review of NDA 22-271, alogliptin and the DSI inspection of the pivotal BE study

Valerie and Hylton,

Did you see the January 19, 2009, submission that responds to our IR letter re: the DSI inspection of the pivotal BE study. B/P says the deficiency did not impact on reliability of BE study results. Was there anything in the AE data?

Sorry to ask, but it's really difficult to know what folks might not have seen when the reviews don't include the dates of submissions reviewed.

Lee

From: Chung, Sang
Sent: Wednesday, June 17, 2009 8:01 AM
To: Ripper, Leah W
Cc: Choe, Sally
Subject: RE: Your review of NDA 22-271, alogliptin and the DSI inspection of the pivotal BE study

Hi Lee,

Thanks for the comments.
Clin Pharm and clinical team received the DSI review and clin pharm concluded that DSI findings

did not impact on reliability of BE study results. The sponsor's response on January 19, 2009 did not include new data to revisit clin pharm review on the BE study results.

Regards,

Sang

<< Message: RE: DFS Email - N 022271 N 000 27-Dec-2007 - Review >> << File: DSI review.pdf >>

From: Ripper, Leah W
Sent: Tuesday, June 16, 2009 7:40 PM
To: Chung, Sang
Cc: Choe, Sally
Subject: RE: Your review of NDA 22-271, alogliptin and the DSI inspection of the pivotal BE study

Sang, I see that we sent out an IR letter dated 10/24/08 re: this DSI inspection. Did you see a response dated January 19, 2009, regarding it?

Lee

From: Ripper, Leah W
Sent: Tuesday, June 16, 2009 6:53 PM
To: Chung, Sang
Subject: Your review of NDA 22-271, alogliptin

Sang,

I am looking at the action package for NDA 22-271, Nesina (alogiptin)

Page 5 of your 8/28/08 review of alogliptin notes that " . . . Commercial formulations were BE to formulations used in Phase 3 studies. Review of the DSI on this pivotal BE study is pending at this time."

Did you ever see DSI report? If not, please look at it and let me know if you think you need to comment on it for the record. The action goal date is June 26
<< File: CDocumen.pdf >>

Thanks, Lee

Lee W. Ripper
Associate Director for Regulatory Affairs
Office of Drug Evaluation II, OND, CDER
Phone: 301-796-1282 / Fax: 301-796-9717
Mailing Address: FDA, CDER, OND, Room 3218
5901-B Ammendale Road
Beltsville, MD 20705-1266

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/s/

Leah Ripper
6/19/2009 04:30:31 PM
CSO

From:	Marchick, Julie
To:	"Idemoto, Christie Ann (TGRD)";
CC:	
Subject:	NDA 22-271 Nesina (alogliptin) - Information Requests
Date:	Wednesday, May 13, 2009 10:38:14 AM
Attachments:	

Hi Christie,

We have three more information requests for you.

1. Please clarify when TZD-009 subject 311/9003's alogliptin was interrupted relative to the liver test abnormalities.

2. Please provide case narratives for subjects with markedly abnormal creatinine (>1.5X baseline) in controlled phase 2/3 clinical trials of alogliptin.

3. Please provide an analysis of pancreatitis cases occurring with alogliptin and comparators in your controlled phase 2/3 clinical trials. Present data by individual study and for the controlled pooled safety population. Include a description of how events were identified.

Would it be possible for you to submit this information by Wednesday, May 20?

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

Julie Marchick
5/13/2009 10:40:36 AM
CSO

From:	Marchick, Julie
To:	"Idemoto, Christie Ann (TGRD)"; "Gupte, Sangeeta (TGRD)";
CC:	
Subject:	NDA 22-271 Alogliptin and NDA 22-246 Alogliptin/ Pioglitazone - Information Requests
Date:	Friday, May 01, 2009 8:01:04 AM
Attachments:	

Good Morning Christie and Sangeeta,

We have the following requests. We ask that you submit the requested information by Wednesday, May 6.

1. Please calculate the number of subjects exposed to alogliptin for >= 6, >=12, and >=18 months. Please include subjects in NDA 22-271's controlled phase 2/3 trials and uncontrolled OLE-012 (up to and including the 120 day safety update) as well as subjects exposed to alogliptin in NDA 22-426 controlled phase 2/3 trials (at the time of NDA 22-426 submission). Please run a second analysis which also includes the NDA 22-426 120 day safety update. Please display data for subjects exposed to alogliptin only. As another analysis, please include subjects in the alogliptin+pioglitazone arm(s) in NDA 22-426. For all analyses, present data by alogliptin dose (explain how you handle patients who switched from 12.5 mg to 25 mg) and for combined alogliptin doses.

2. Please rerun the same analyses in (1) above and show the data by category of renal impairment (mild, moderate, or severe renal impairment), using the Cockcroft-Gault method for one analysis and the MDRD formula as another analysis. For these renal analyses, please run one set of analyses including OL-012 and another set of analysis excluding OL-012.

Please let me know if you have any questions.

Thanks,
Julie

Julie Marchick

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
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/s/

Julie Marchick
5/1/2009 08:03:46 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-271

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

We also refer to your March 10, 2009, correspondence, received March 11, 2009, requesting a meeting to discuss your proposed cardiovascular outcome protocol.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	Monday, April 27, 2009
Time:	3:00 – 4:00 P.M.
Location:	FDA, White Oak, Federal Research Center 10903 New Hampshire Avenue, Building 22 Silver Spring, MD 20993

CDER participants (tentative):

Curtis Rosebraugh, MD	Director, Office of Drug Evaluation II
Mary Parks, MD	Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, MD, MMSc	Clinical Team Leader, DMEP
Valerie Pratt, MD	Clinical Reviewer
J.Todd Sahlroot, PhD	Deputy Division Director, Office of Biostatistics
Janice Derr, PhD	Reviewer, Office of Biostatistics
Lina AlJuburi, PharmD, MS	Chief, Project Management Staff
Julie Marchick MPH	Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at julie.marchick@fda.hhs.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to

request an escort to the conference room: Julie Marchick, 301-796-1280; or the division secretary, 301-796-2290.

Provide the background information for this meeting (electronic copy to the NDA and nine desk copies to me) at least two weeks prior to the meeting. Please note that each copy of the background information document should be one volume that is no more than one inch thick. The meeting packages should be sent to:

CDR/CDER/FDA
Division of Metabolism and Endocrinology Products (DMEP)
ATTN: Julie Marchick
5901-B Ammendale Road
Beltsville, MD 20705-1266

If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by April 13, 2009, we may cancel or reschedule the meeting.
If you have any questions, please call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Marchick
3/13/2009 07:47:35 AM

Aljuburi, Lina

From: Aljuburi, Lina
Sent: Tuesday, February 24, 2009 3:03 PM
To: 'Christie Ann Idemoto (cidemoto@tgrd.com)'
Cc: Marchick, Julie
Subject: NDA 22-271 alogliptin information request

Hi Christie,

Julie is out-of-the-office this week, so I'm sending you an information request for NDA 22-271 alogliptin on her behalf.

Please clarify why NDA 22-271 table 8.4.6.1 lists 23 alogliptin cardiac TESAEs: 2 placebo cardiac TESAEs whereas table 10.b only lists 24 cardiac SAEs. Please provide the missing narratives that are described in table 8.4.6.1 but not provided in table 10.b (i.e. possibly the cases of hypertensive heart disease and palpitations).

In addition, please provide the narratives for the following adverse events which were included in the January 2009 MACE analysis:

SULF-007:	104/7016, 244/7001
MET-008:	315/8016
TZD-009:	452/9004, 246/9002
INS-011:	447/5009
OPI-001:	888/3029, 725/3005, 694/3017, 716/3021, 728/3008
OPI-002:	053/2513, 673/2501, 291/2501, 741/2506, 067/2506

Feel free to contact me if you have questions regarding these requests.

Many thanks,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

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/s/

Lina Aljuburi
2/24/2009 03:06:08 PM
CSO

From: Marchick, Julie
To: "Idemoto, Christie Ann (TGRD)";
CC: Aljuburi, Lina;
Subject: RE: Information Request Letter
Date: Wednesday, January 14, 2009 7:47:06 AM
Attachments:

Good Morning Christie,

We agree with all of your comments and proposals raised in your email below. Please feel free to contact Lina or me if you have additional questions.

Thanks,
Julie

From: Idemoto, Christie Ann (TGRD) [mailto:cidemoto@tgrd.com]
Sent: Monday, January 12, 2009 3:43 PM
To: Aljuburi, Lina; Marchick, Julie
Subject: RE: Information Request Letter

Hi Lina, and Julie,

We appreciate you providing us with the information request letter as soon as it became available. In order to ensure we meet the FDA's requests by Jan 21, we want to be clear on your specific requests and therefore have several clarifying questions, as detailed below. Your clarification is needed as soon as possible in order for us to begin working in your requests and meeting your deadline by January 21. Please let me know if the Division can provide responses to our questions before the close of business tomorrow, Tuesday (Jan 13). Thanks in advance.

1. In reference to Part I, TGRD will be presenting the requested analyses for all controlled Phase 2 and Phase 3 studies submitted to the original NDA (studies 003, 007, 008, 009, 010, and 011) and the alogliptin/pioglitazone FDC NDA (studies 001 and 002), which is consistent with the studies included in our cardiovascular amendment. For Part 1.B, TGRD would like to clarify that since neither the original NDA nor the FDC NDA included any unblinded controlled studies or study extensions, this additional analysis population is not applicable to our application. Please advise if the Division requires any additional clarification.

2. In reference to Part III.A, although cardiovascular death is not identified as such by a MedDRA preferred term in our database, the event leading to death is captured as a preferred term. For the listing identified as Table 1, TGRD would propose to list the actual preferred term for these events and to flag the events that were considered cardiovascular death. Please confirm that this is acceptable.

3. In reference to Part III.A, the SMQ MACE and custom MACE events to be captured will be those with an onset date between the date of first dose and the date of last dose plus 14 days (inclusive) per the treatment emergent period defined in the original statistical analysis plans. Please note that the total number of cardiovascular deaths summarized will be 4, not 5, as one cardiovascular death in study 008 occurred 19 days after the date of last dose.

4. In reference to Part III.B.1, specifically example Table 2, for controlled Phase 3 studies submitted as part of the original NDA (studies 003, 007, 008, 009, 010, and 011), since alogliptin placebo was compared to active alogliptin on a stable background therapy in each study, TGRD proposes to summarize the data for each study as Placebo Comparator versus the individual alogliptin doses (12.5 mg or 25 mg in Phase 3 and 6.25 mg, 12.5 mg, 25 mg, 50 mg, or 100 mg in Phase 2).

   For FDC study 001 submitted as part of the alogliptin/pioglitazone FDC NDA, although subjects were randomized to receive both alogliptin (placebo or active) and pioglitazone (placebo or active) in a 12-arm full factorial design, the intent of the trial was to assess the safety and efficacy of alogliptin added onto pioglitazone. As a result, TGRD proposes to summarize the data in 3 pooled groups as Placebo Comparator (ie, alogliptin placebo with or without pioglitazone) versus the individual alogliptin doses (12.5 mg or 25 mg with or without pioglitazone).

   Finally, for FDC study 002 submitted as part of the alogliptin/pioglitazone FDC NDA, in order to maintain consistency with study 001, TGRD proposes to summarize the data in 3 pooled groups as Placebo Comparator (ie, alogliptin placebo with pioglitazone 25 mg), alogliptin 12.5 mg (with pioglitazone 30 mg), and alogliptin 25 mg (with pioglitazone placebo or pioglitazone 30 mg).

   The proposed mapping of randomized treatments by study is summarized in the following table. Note that no treatment groups will be mapped to Active Comparator. Please confirm that this presentation is acceptable for the listing identified as Table 2 in the information request letter.

Proposed Randomized Treatment Mapping by Study

Study	Placebo Comparator	Alogliptin 6.25 mg	Alogliptin 12.5 mg	Alogliptin 25 mg	Alogliptin 50 mg	Alogliptin 100 mg	Active Comparator
001	A0 + P0 A0 + P15 A0 + P30 A0 + P45		A12.5 + P0 A12.5 + P15 A12.5 + P30 A12.5 + P45	A25 + P0 A25 + P15 A25 + P30 A25 + P45			
002	A0 + P30		A12.5 + P30	A25 + P0 A25 + P30			
003	A0	A6.25	A12.5	A25	A50	A100	
007	A0		A12.5	A25			
008	A0		A12.5	A25			
009	A0		A12.5	A25			
010	A0		A12.5	A25			
011	A0		A12.5	A25			

Note: In each cell, the randomized alogliptin and pioglitazone doses are denoted by Ax and Py, where x and y are the randomized doses, respectively. A dose of zero (ie "0") indicates placebo. An empty cell indicates that no randomized treatment group will be mapped from the given study.

5. In reference to Part E, please confirm that the extension study referred to in the dataset variable "Participated in extension study (Yes/No)" refers to the study type mentioned in Part I.B. If our assumption is correct, this column will not appear in the electronic dataset. In addition, the variable "Indicator for whether or not the event took place during the double blind period" will not be included, since none of our studies included an unblinded controlled period.

Christie Ann Idemoto
Takeda Global Research & Development Center, Inc.
675 N. Field Drive
Lake Forest, Illinois 60045
p: 847-582-3506
c: (b) (6)
e: cidemoto@tgrd.com

From: Aljuburi, Lina [mailto:l.aljuburi@fda.hhs.gov]
Sent: Sunday, January 11, 2009 12:39 PM
To: Idemoto, Christie Ann (TGRD); Pritza, Mary Jo (TGRD)
Cc: Marchick, Julie
Subject: Information Request Letter

Happy New Year, Christie and Mary Jo!

Please see attached information request letter regarding NDA 22-271 alogliptin.
There is a relatively short turnaround time for your response - by Wednesday, January 21, 2009.
So we wanted to make sure we got a copy of the letter to you just as soon as poss ble.

<<Alogliptin_MACE_IR_01.09.09.pdf>>

Feel free to contact Julie or me if you have any questions.

Please confirm receipt of this email.

All the best for 2009,
Lina

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

l.aljuburi@fda.hhs.gov
301-796-1168 (phone)
301-796-9712 (fax)

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Julie Marchick
1/14/2009 08:52:18 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, M.S.
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, Illinois 60045-4832

Dear Ms. Idemoto:

Please refer to your December 27, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

In anticipation of the upcoming Advisory Committee meeting for your product, we request that you submit for our review the following data regarding major adverse cardiovascular events (MACE).

Submit the requested no later than January 21, 2009, to ensure that there is sufficient time for review.

Please provide information and analyses regarding MACE events as follows:

I. Analysis population(s):

A. The main analysis population should include the randomized, double-blind, controlled periods for all completed Phase 2 and Phase 3 trials of your product.

B. An additional analysis population should include the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of your product. That is, include unblinded periods if they remain controlled, and include controlled data past the primary HbA1c efficacy measurement, if applicable. Do not include uncontrolled extension periods.

II. Endpoints: Use the following two endpoints, which will be referred to hereafter as "SMQ MACE" and "Custom MACE". We acknowledge that there may be many opinions about what precise terms should be included in these endpoints, but these are the terms we want you to use. For nonfatal events, use MedDRA Preferred Terms as they were originally assigned in your NDA submission. Do not use post hoc adjudication for nonfatal events. Adjudication of cardiovascular deaths is acceptable. Do not add or subtract Preferred Terms from either endpoint. If you wish to provide separate analyses with independent external post hoc

adjudication of nonfatal events from the specified endpoints, you may do so, but you must submit the analyses with unadjudicated Preferred Terms for nonfatal events as requested.

"SMQ MACE": Use a composite endpoint of cardiovascular death, and all Preferred Terms in the Standardised MedDRA Queries for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents".

"Custom MACE": Use a composite endpoint of cardiovascular death and the following MedDRA Preferred Terms:

- Acute myocardial infarction
- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Coronary artery thrombosis
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Postprocedural stroke
- Silent myocardial infarction
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

III. Types of Analyses

A. Listing

List all events (including those from uncontrolled portions of the trials) from both the "SMQ MACE" and the "Custom MACE" endpoints, including both the first event observed and any subsequent events observed. The listing should be sorted by treatment group and patient ID. For patients with multiple events, the events should be listed in order of occurrence. The events should be defined by MedDRA Preferred Terms. A proposed format for this listing is shown below:

Table 1 (example) Listing of MACE events sorted by treatment group and type of event for all studies

Pt ID	Study	Treatment	MedDRA Preferred Term	Date of event	Time on study at time of event	In the main analysis population?	Serious event?	SMQ MACE?	Custom MACE?

B. Summaries

1. Summary of the incidence of SMQ MACE and Custom MACE events in the main analysis population and in the additional analysis populations by dose of the study drug. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 2 (example) Incidence of SMQ MACE events in the main analysis population, by dose of study drug

	Dose 1	Dose 2	Dose 3	All Doses	Placebo Comparator	Active Comparator
Pooled	x/X (y%)					
Study 1						
Study 2						
Study 3						
Study 4						

x= number of events for that group
X=total number of randomized patients in the safety database for that group
y=x/X times 100

2. Summaries of the incidence of SMQ MACE events and Custom MACE events in the main analysis population and the additional analysis population, combined across doses of the study drug in separate tables. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE events and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 3 (example) Incidence of SMQ MACE events in the main analysis population, combined across doses of study drug, reported separately by study

Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (events/N)	Incidence ratio, 95% CI	Incidence difference, 95% CI	Incidence rate (events/Pt-yrs)	Incidence rate ratio, 95% CI	Incidence rate difference, 95% CI
Study 1	Study Drug									
	Active Comparator									
	Placebo Comparator									
Study 2	Study Drug									
	Active Comparator									
	Placebo Comparator									
etc	etc									
etc	etc									
Overall results stratified by study										

C. Analyses

For SMQ MACE and custom MACE, analyze both the incidence (events/N) and the incidence rate (events/patient-year) using the analysis populations described under I. A. and B. of this document. If the set of Phase 2 and 3 studies has more than one type of comparator group, we recommend making three comparisons: a) the study drug compared to the placebo; b) the study drug compared to the active comparator; and c) the study drug compared to the placebo and the active comparator groups combined. Analysis c) is the analysis that should be presented in the last line of Table 3 and the Forest plots discussed in Section D.

The analyses should be stratified by study and we recommend that a stratified exact method be included as one of the analyses. However, we acknowledge that multiple studies may have 0

MACE events in one or more groups and that pooling studies for an unstratified analysis may be a reasonable alternative.

D. Forest Plots

For SMQ MACE and custom MACE, provide a forest plot depicting the incidence ratio results from the individual studies and the results from the overall stratified analysis for the primary analysis population described in I. A.

E. Electronic Data Files

Please provide a dataset with a single observation for each patient which includes the following:

- Study identifier
- Unique patient identifier
- Demographic data
- Date of randomization
- Treatment group
- Date of completion/rescue/discontinuation of the randomized, controlled, double-blind period of the study
- Exposure time in the randomized, controlled, double-blind period of the study
- Participated in extension study (Yes/No)
- For each of the composite endpoints (”SMQ MACE” and “Custom MACE”), include the following set of variables:
    a) Duration of time from randomization to date of first event or censoring
    b) Indicator for whether or not the event took place during the double blind period
    c) Censoring variable
    d) Date of event or censoring
- MedDRA Preferred Term for “SMQ MACE”
- MedDRA Preferred Term for “Custom MACE”

If you have any questions, call Julie Marchick, M.P.H., Regulatory Project Manager, at 301-796-1280.

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/

Hylton Joffe
1/11/2009 01:28:01 PM
Hylton Joffe for Mary Parks

MEMORANDUM

DATE: November 6, 2008

SUBJECT: Response to FDA Request for Information

TO: File to NDA #22-271 [Nesina (alogliptin) Tablets]

FROM: Chien-Hua Niu, Ph.D.

THROUGH: Dr. Ali Al Hakim, Branch Chief, Branch II/DPMA-1/ONDQA

The purpose of the 10/16/2008 amendment is (1) to provide a more detailed description of the process used for isolation and/or synthesis of the [redacted] (b) (4) substance standards and (2) to include the requirements for evaluation of [redacted] (b) (4) in the drug product stability specification.

(1). All seven known [redacted] (b) (4) substances, including [redacted] (b) (4) have been chemically synthesized and structurally characterized by NMR and MS (see pp. 36 to 60 in Section 3.2.S.3.2 "Characterization: Impurities" of the 10/16/2008 amendment.

For [redacted] (b) (4) the chiral HPLC analysis was performed. The measured retention time of [redacted] (b) (4) did not match that of the [redacted] (b) (4)

(2). Regarding evaluation of [redacted] (b) (4) in the drug product, Takeda will continue stability testing for pilot-scale primary stability batches, the three commercial-scale validation batches and future production batches of alogliptin tablets ([redacted] (b) (4), 6.25 mg, 12.5 mg and 25 mg). Additional data from the studies will be submitted either in NDA updates or in annual NDA reports.

Protocols for stability studies of pilot-scale batches, validation batches, production batches, and annual batches are shown on pages 4 to 7 in Section "Stability: Post-Approval Stability Protocol and Stability Commitment" of the 10/16/2008 amendment.

Conclusion: Adequate information is provided. No action is indicated.

cc: Julie Marchick, Project Manager, HFD-510
NDA22271MEM1

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/s/

Chien-Hua Niu
11/6/2008 12:58:57 PM
CHEMIST
Adequate CMC information is provided. No action is indicated.

Ali Al-Hakim
11/6/2008 01:07:05 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045-4832

Dear Ms. Idemoto:

Please refer to your December 27, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide a Major Adverse Cardiovascular Events (MACE) meta-analysis (cardiovascular death, nonfatal myocardial infarction, and stroke) of all completed Phase 2 and 3 trials for alogliptin, that is updated to incorporate the alogliptin + pioglitazone trials. Please express the data as number of people with events and provide both the total number of randomized patients and the patient-year exposure for the various treatment groups, both by individual study and combined across studies. Please also provide information on the incidence of the endpoint by alogliptin dose and show the numbers both by individual study and pooled. Please calculate the risk ratio with 95% confidence interval for the combined data from placebo-controlled trials and add-on trials (drug vs. placebo, each added to standard therapy).

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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 Parks
11/5/2008 03:32:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Mr. Jeff Soderquist
Vice President Quality Assurance and Compliance
Takeda Global Research and Development Center
One Takeda parkway
Deerfield, Illinois 60015

Dear Mr. Soderquist:

Between July 8 and 14, 2008, Ms. Susan Yuscius, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct as the sponsor of the following clinical investigations of the investigational drug alogliptin (Nesina):

A. SYR-322-SULF-007 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR-322 When Used in Combination with Sulfonylurea in Subjects with Type 2 Diabetes"
B. SYR-322-MET-008 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR-322 When Used in Combination with Metformin in Subjects with Type 2 Diabetes"
C. SYR-322-TZD-009 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Pioglitazone in Subjects with Type 2 Diabetes"
D. SYR-322-PLC-010 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) Compared with Placebo in Subjects with Type 2 Diabetes"
E. SYR-322-INS-011 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Insulin in Subjects with Type 2 Diabetes"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Yuscius during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

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/s/

Constance Lewin
10/1/2008 01:32:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
675 N. Field Drive
Lake Forest, Illinois 60045-4832

Dear Ms. Idemoto:

Please refer to your December 27, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

The Division of Scientific Investigations (DSI) audited the clinical facility (MDS Pharma Services in Phoenix, Arizona) and the analytical facility [redacted] (b) (4) where study SYR-322-027, entitled *An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalency of the Phase 3 SYR-322 Tablets (12.5 mg and 25 mg) with the Commercial SYR-322 Tablets (12.5 mg and 25 mg) in Healthy Adult Subjects* was conducted.

DSI concluded that there were inaccuracies in reporting adverse events (AEs) and urine collection times and volumes in the case report forms (CRFs). For example, 2 of the 28 subjects reviewed had adverse events documented on the general physical examination (source) but not reported on the case report form (Subjects 0001/006 and 0001/101). Four of the 46 source documents and/or case report forms reviewed had transcription errors noted for the urine collection times and/or total volume collected (Subjects 0001/059, 0001/066, 0001/070, and 0001/083). Because the data audited were limited, we request that you provide an accurate list of AEs and urine collection times and volumes for all participants in the study.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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 Parks
10/24/2008 01:01:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

Please refer to your December 27, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets. We also refer to your responses, emailed on August 22, 2008, to our letter dated August 19, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Include (b) (4) in the drug product stability specification because your currently available stability data are too limited to support your proposal to omit this testing.

2. Based on the information submitted in the NDA, your proposal to submit CBE-0 post-approval supplements for changes in the manufacturing sites for the drug substance and/or drug product, changes that may involve changes in the manufacturing processes, is not acceptable at this time. Such a change should be submitted to FDA as a prior-approval supplement because the review timeline for a CBE-0 supplement would not allow adequate time for FDA to determine the CGMP status of a new manufacturing site. Our more recent experience has been that information on the CGMP status of a manufacturing site as provided by an applicant cannot be relied upon for our regulatory decision.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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 Parks
8/25/2008 04:11:26 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

Please refer to your December 27, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alogliptin tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. Drug Substance:

1. Regarding Impurity Reference Standard:

a. As mentioned on page 9 in Section 3.2.S.5 "Reference Standards or Materials", SYR-322 (b) (4) has been characterized by IR and optical rotation. The results indicate that (b) (4) However, Table 1 (page 4 of the same Section) shows that (b) (4) Explain why the optical rotation of (b) (4) is not close to (b) (4)

b. Section 3.2.S.3.2 "Characterization: Impurities" indicates that the (b) (4) substance standards, including (b) (4) were characterized. Provide information on how these impurity standards are obtained. If they are chemically synthesized, a brief description on how they are prepared should be submitted.

B. Drug Product:

1. Regarding Specifications:

Results from stability studies indicate that the (b) (4) is correlated with the (b) (4) of related substances in

alogliptin tablets, especially in the 6.25 mg tablets. Therefore, (b) (4) testing and acceptance criteria should be included in the specifications for alogliptin tablets and this attribute should continue to be monitored for all packaging configurations when stored long term conditions (25ºC/60% RH) and accelerated conditions (40ºC/75% RH).

2. **Regarding Validation of Analytical Procedures:**

   Explain why the detection limit/quantitation limit (LOD/LOQ) of the HPLC system used for the determination of content uniformity and assay is not included in Analytical Method Validation for SYR-322 Tablets (see Section 3.2.P.5 "Validation of Analytical Procedures" "Method SYR-322/00322").

3. **Regarding Stability:**

   The postapproval stability commitment should include reporting the stability results of the primary stability lots as well as commercial lots in the annual reports.

4. **Regarding Comparability Protocols:**

   Any changes in the manufacturing sites for the drug substance and drug product can be implemented after approval of a post-approval supplemental application for the NDA and a satisfactory cGMP status verified by the FDA Office of Compliance.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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 Parks
8/19/2008 07:06:28 PM

Executive CAC
Date of Meeting: August 5, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Bayo Laniyonu, Ph.D., DMIHP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader
David Carlson, Ph.D., DMEP, Presenting Reviewer

Author of Minutes: David Carlson, Ph.D., DMEP

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

NDA #: 22-271
Drug Name: Alogliptin (Nesina™ / SYR-322)
Sponsor: Takeda

Background

Mouse Carcinogenicity Study

The final study report of a GLP-compliant, standard two year oral (gavage) carcinogenicity in CD-1 mice was reviewed and results were discussed at a meeting of the Executive Carcinogenicity Assessment Committee (ECAC). The doses were higher than those proposed by the ECAC, but the high dose did not result in remarkable toxicity and the study was considered acceptable.

Key study findings: NOAEL = 300 mg/kg/day (non-neoplastic and neoplastic findings); 60X MRHD. Notable findings were limited to a 5% incidence of benign hepatocellular adenomas in high dose females (74X MRHD), which was within the historical control range and not statistically significant when considered a "common tumor". The finding was not considered drug-related.

Rat Carcinogenicity Study

The final study report of a GLP-compliant, standard two year oral (gavage) carcinogenicity in Sprague-Dawley rats was reviewed and results were discussed at a meeting of the ECAC. The study was considered acceptable based on prior ECAC concurrence on the doses and evidence the high dose reached MTD due to 18-22% decreased body weights.

Key study findings: NOAEL = 75 mg/kg/day (32X MRHD). The combined incidence of thyroid C-cell adenomas and carcinomas was increased in male rats at SYR-322 exposures (AUC) that were 288- and 533-fold higher than the MRHD. There were no

drug related neoplasms in females. SYR-322 poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (32X) and very high exposure multiples (≥ 288X) at doses that caused increased combined thyroid C-cell adenomas and carcinomas in males.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed the study was adequate.
- The Committee concurred that the study was negative for drug-related neoplasms.

Rat:

- The Committee agreed the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded the study was positive for the drug-related effect of combined thyroid C-cell adenomas and carcinomas in male rats at a large multiple (≥ 288X) of the expected maximum human exposure. No drug-related neoplasms were seen at a lower dose that provided 32-fold higher exposure than the expected maximum human exposure.

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

cc:\

NDA 22-271/Division File, DMEP
Todd Bourcier/Team leader, DMEP
David Carlson/Reviewer, DMEP
Julie Marchick/PM, DMEP
ASeifried, OND IO

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/s/

David Jacobson-Kram
8/7/2008 02:58:13 PM

From:	Marchick, Julie
To:	Idemoto, Christie Ann (TGRD);
CC:	"Pritza, Mary Jo (TGRD)";
Subject:	NDA 22-271 Alogliptin - Information Requests - Cardiovascular and Renal Adverse Events
Date:	Friday, June 13, 2008 1:40:47 PM
Attachments:	

Hi Christie,

We have the following additional information requests:

1. Please provide a table (in pdf or Word) listing all patients with a treatment-emergent deterioration in **serum creatinine, as defined as a 10% increase in serum creatinine from baseline**. Please include patients who have an increase in serum creatinine such that a **followup creatinine value** during the clinical study **exceeds 1.1x the baseline value**:

Please provide data in the table sorted by study and treatment groups (placebo and alogliptin by dose) for the controlled Phase 2 and Phase 3 studies (Studies 003, 007, 008, 009, 010, 011).

- Patient ID #
- age/sex
- known duration of type 2 diabetes mellitus
- study
- treatment
- baseline serum creatinine
- change in serum creatinine
- baseline urine albumin/creatinine ratio
- change in urine albumin/creatinine ratio
- baseline renal impairment level, as assessed by Cockcroft-Gault equation
- change from baseline renal impairment level, as assessed by Cockcroft-Gault equation
- baseline renal impairment level, as assessed by MDRD equation
- change from baseline renal impairment level, as assessed by MDRD

equation

Please also provide an EXCEL table electronically with the data requested in question 1.

2. For the post-baseline creatinine elevations reported in Question 1, please provide the following additional information:

Please provide the time point at which the increase was observed and subsequent creatinine values for each patient to determine if there is an isolated increase, a sustained increase, or variability over the duration of the study.

3. Please expand Table 1, which you submitted on May 9, 2008 in response to Question 4 in the FDA April 18, 2008 information request with the following **additional** information.

For the controlled phase 2/3 database, please provide **the following population data** by treatment group (for alogliptin, present the data by dose and for pooled doses) the number of patients **(n, %)** with baseline and endpoint creatinine values who had changes that meet the following criteria in **serum creatinine:**

A. **Any** increase in serum creatinine value from baseline measurement to post-baseline measurement
B. post-baseline value ≥1.1x the baseline value
C. post-baseline value ≥1.2x the baseline value

4. Please provide the expanded Table 1, as requested in question 3, in an EXCEL table, electronically.

5. Please provide Table 2 "*Listing of Subjects with Treatment-Emergent Heart Rate and Rhythm-Related Cardiac Adverse Events, by Preferred Term and Treatment – Phase 2 and Phase 3 Controlled Studies",* which was executed 07MAY2008 16:28, and submitted in response to FDA's April 18 Information Request on May 9, 2008, as an EXCEL table, electronically.

6. Please provide Table 3 "*Listing of Subjects with Treatment-Emergent Ischemia-Related Cardiac Adverse Events, by Preferred Term and Treatment – Phase 2 and Phase 3 Controlled Studies",* which was executed 07MAY2008

16:28, and submitted in response to FDA's April 18 Information Request on May 9, 2008, as an EXCEL table, electronically.

7. Please provide Table 4 "*MACE Analysis– Phase 2 and Phase 3 Controlled Studies",* which was also submitted in response to FDA's April 18 Information Request on May 9, 2008, as an EXCEL table, electronically.

8. Please provide listing of *"IND 69,707 and IND 73,193: Ongoing and Planned Studies with Alogliptin"* which was also submitted in response to FDA's April 18 Information Request on May 9, 2008, as an EXCEL table, electronically.

Let me know if you have any questions.

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

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/s/

Julie Marchick
6/13/2008 03:08:25 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271 **INFORMATION REQUEST LETTER**

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

Please refer to your December 27, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nesina (alogliptin) Tablets.

We are reviewing the Clinical and Clinical Pharmacology sections of your NDA and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide **narratives and case report forms** for all patients with non-serious cardiac adverse events. Please also include potential cardiac preferred terms that may have been classified under other System-Organ Classes (SOCs), such as "chest pain". Please sort narrative information by study and treatment groups (placebo and alogliptin, by dose).

2. Please provide a WORD table with the following information for all patients with **serious** treatment-emergent cardiac events in controlled Phase 2 and Phase 3 studies (Studies 003, 007, 008, 009, 010, 011.) Please also include potential cardiac preferred terms that may have been classified under other SOCs (e.g., "chest pain"). Please sort information in table by study and treatment groups (placebo and alogliptin, by dose).
   - Patient ID #
   - age/sex
   - known duration of type 2 diabetes mellitus
   - study
   - treatment
   - day of study
   - cardiac serious adverse event
   - baseline serum creatinine
   - change in serum creatinine

3. Please provide a WORD table with the following information for all patients with **non-serious** treatment-emergent cardiac events in controlled Phase 2 and Phase 3 studies (Studies 003, 007, 008, 009, 010, 011). Please also include potential cardiac preferred terms that may have been

classified under other SOCs (e.g., "chest pain"). Please sort information in table by study and treatment groups (placebo and alogliptin, by dose).

- Patient ID #
- age/sex
- known duration of type 2 diabetes mellitus
- study
- treatment
- day of study
- cardiac non-serious adverse event
- baseline serum creatinine
- change in serum creatinine

4. For the controlled phase 2/3 database, please provide **the following population data** by treatment group (for alogliptin, present the data by dose and for pooled doses) for serum creatinine, urine albumin/creatinine ratio, and glomerular filtration rate (GFR) estimated by the Cockcroft-Gault and MDRD equations:
   i. the number of patients randomized to study medication,
   ii. the number of patients (n, %) with baseline <u>and</u> endpoint (or post-baseline) values for each of the above variables, and
   iii. the number of patients (n, %) with changes that meet the following criteria:

- **For serum creatinine and urine albumin/creatinine ratio:**
  i. Shift in value from the normal range to high
  ii. post-baseline value ≥1.25x the baseline value
  iii. post-baseline value ≥1.5x the baseline value
  iv. post-baseline value ≥2x the baseline value
  v. post-baseline value ≥3x the baseline value
  vi. post-baseline value ≥1.25x ULN
  vii. post-baseline value ≥1.5x ULN
  viii. post-baseline value ≥2x ULN
  ix. post-baseline value ≥3x ULN
  x. post-baseline value ≥5x ULN

- **For GFR (**estimated by both the Cockcroft-Gault and MDRD equations):
  i. mean change (with SD) from baseline to study end
  ii. median change (with interquartile range) from baseline to study end
  iii. shift in value from the normal range to low
  iv. shift from normal renal function to mild renal impairment
  v. shift from normal renal function to moderate renal impairment
  vi. shift from mild renal function to moderate renal impairment
  vii. baseline value ≥1.25x post-baseline value
  viii. baseline value ≥1.5x post-baseline value
  ix. baseline value ≥2x post-baseline value
  x. baseline value ≥3x post-baseline value
  xi. post-baseline value ≤80 mL/min
  xii. post-baseline value ≤50 mL/min
  xiii. post-baseline value ≤30 mL/min

5. Please clarify the data in the following table (Table 3.k. Changes from Baseline to Endpoint in Urinalysis Variables in the Controlled Phase 2 and 3 Study Group.)
   - Why is the baseline n for the urine albumin/creatinine ratio variable substantially smaller than the baseline n for the specific gravity and pH?
   - What accounts for the differences in the sample sizes for "baseline", "endpoint", and "endpoint change from baseline" for the urine albumin/creatinine ratio?
   - Is the 'mean change from baseline' calculated from the 'endpoint change from baseline (n)' population?
   - Please calculate medians and interquartile ranges for the urine albumin/creatinine ratio data in the table below.

Table 3.k Changes from Baseline to Endpoint in Urinalysis Variables in the Controlled Phase 2 and 3 Study Group

		Alogliptin	
Urinalysis Variable	**Placebo N=534**	**12.5 mg N=922**	**25 mg N=910**
Specific Gravity			
Baseline (n)	534	922	910
Baseline mean (SD)	1.0215 (0.00712)	1.0217 (0.00697)	1.0217 (0.00659)
Endpoint (n)	514	883	870
Endpoint mean (SD)	1.0224 (0.00742)	1.0217 (0.00700)	1.0211 (0.00672)
Endpoint change from Baseline (n)	514	883	870
Mean change from Baseline (SD)	0.0009 (0.00742)	0.0000 (0.00693)	-0.0004 (0.00668)
Urine Albumin/Creatinine Ratio (µg/mg)			
Baseline (n)	381	633	617
Baseline mean (SD)	71.2 (165.22)	85.3 (235.92)	80.9 (179.57)
Endpoint (n)	295	493	486
Endpoint mean (SD)	76.3 (174.27)	115.4 (430.13)	96.0 (287.79)
Endpoint change from Baseline (n)	245	432	409
Mean change from Baseline (SD)	-8.4 (184.09)	22.0 (469.38)	15.2 (298.29)
pH			
Baseline (n)	534	922	910
Baseline mean (SD)	5.40 (0.494)	5.44 (0.504)	5.42 (0.490)
Endpoint (n)	514	883	869
Endpoint mean (SD)	5.46 (0.520)	5.51 (0.493)	5.49 (0.498)
Endpoint change from Baseline (n)	514	883	870
Mean change from Baseline (SD)	0.05 (0.579)	0.07 (0.570)	0.06 (0.615)

Source: IAS End-of Text Table 8.5.1.1.3.

6. Please clarify the methodology used to perform the cardiac cluster analyses (e.g., the "ischemia-related" and "heart rate/rhythm-related" analyses). For example, how did you decide that a given event was ischemia-related? Was this determination made in a blinded fashion? Which preferred terms were included in the "ischemia-related" category? etc. Please submit a detailed explanation of how you performed these cluster analyses. This response should include a list of patients and preferred terms that were included in each of these cluster categories.

7. Please conduct a MACE analysis (cardiovascular-death, non-fatal myocardial infarction, and stroke) on the controlled phase 2/3 database. Please express the data as number of people with events and provide both the total number of randomized patients and the patient-year exposure for the various treatment groups.

8. Please submit a summary table of all planned and ongoing studies (including expected completion dates) if this is not included in the NDA already. If the information is in the NDA, please indicate where it is located.

9. Please provide narratives and case report forms for all patients with non-serious and serious **cerebrovascular** adverse events that may be consistent with stroke. Please explain how you selected these adverse events. Please sort narrative information by study, treatment groups (placebo and alogliptin, by dose), and coding as a serious or non-serious adverse event.

10. The study report for SYR-322-003 indicates plasma concentrations of alogliptin were measured and have also been reported in this .pdf document. We cannot locate the plasma concentration of alogliptin for this study. If you have submitted a data file that contains the subject ID, time after first dose, time after last dose, study day, dose amount, and plasma concentration of alogliptin, please indicate where we may find this information. Otherwise, please provide the following data set: subject ID, time after first dose, time after last dose, study day, dose amount, plasma concentration of alogliptin, creatinine clearance, body weight, age, gender, baseline HbA1c levels, HbA1c levels, change from baseline in HbA1c levels, Baseline Fasting Plasma Glucose, and Fasting Plasma Glucose, Treatment Prior to Washout before study, and DPP-4 inhibition data.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

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 Parks
4/18/2008 01:29:39 PM

Memo to File

NDA: 22-271
Drug: Nesina (alogliptin, SYR-322) Tablets
Sponsor: Takeda Global Research and Development
Subject: Review of Thorough QT Study

On December 27, 2008, Takeda Global Research and Development submitted NDA 22-271 for Nesina (alogliptin) Tablets. This NDA included the final study report for study SYR-322-019, entitled *A Single-Blind, Randomized, Parallel Trial to Define the ECG Effects of SYR-322 Using a Clinical and Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women.*

The Interdisciplinary Review Team for QT Studies (IRT QT Team) reviewed the final study report for study SYR-322-019 under IND 69,707. The IRT QT Team review is dated June 1, 2007.

Regulatory Project Manager: Julie Marchick, MPH

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/s/

Julie Marchick
3/14/2008 11:24:27 AM
CSO

From:	Marchick, Julie
To:	"Idemoto, Christie Ann (TGRD)";
CC:	
Subject:	NDA 22-271 Nesina - PLR Format Review and Items Requested for QTc Protocol Review
Date:	Tuesday, March 11, 2008 10:43:53 AM
Attachments:	PLR Format Review Comments.pdf HighlightsofClinicalPharmacology.doc

---

Good Morning Christie,

We have completed the initial format review of your proposed package insert. Please see the attached document listing our comments. We request that you submit an updated proposed package insert by May 16, 2008.

Also, the Agency's QT Review Team will review your QTc study report, SYR-322-019. In order to review this study report, the QT Review Team will need the following items. Please submit the following items, or if the items have previously been submitted, indicate where they can be found. We request that you submit these items by April 15, 2008.

1. Investigator's Brochure
2. Electronic datasets as SAS transport files (in CDISC SDT format, if possible) and all the SAS codes for the analyses.

3. Narrative summaries and CRFs for any of the following that occur in this QT study:
    a. Death
    b. Serious adverse event
    c. Ventricular tachycardia or fibrillation
    d. Syncope
    e. Seizure
    f. Adverse event resulting in a subject discontinuing from the study
4. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
5. A completed Highlights of Clinical Pharmacology Table (template attached)

Please contact me if you have any questions.

Thanks,
Julie

Julie Marchick
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
301-796-1280 (phone)
301-796-9712 (fax)
julie.marchick@fda.hhs.gov

NDA 22-271 - Nesina (alogliptin) Tablets
PLR Format Review

Please address the identified issues and re-submit labeling by May 16, 2008. This updated version of labeling will be used for further labeling discussions.

Highlights

Dosage and Administration

- Do not use (b) (4) in Highlights (b) (4)

(b) (4)

End of Highlights

- For a new NDA, the revision date will be the month/year that the application is approved. The preferred format is "Revised: Month Year" or "Revised: Month/Year".

(b) (4)

FPI

- All headings and subheadings must be highlighted by bold type that prominently distinguishes the headings and subheadings from other labeling information. Therefore, for other labeling information, use bold type sparingly.

17 Patient Counseling Information

- There is no requirement that the (b) (4) be a subsection under the Patient Counseling Information section. (b) (4)

General

- Remove the header and footer from each page

Additional (Non-PLR-Related) Comments

The Division is requesting changes to the labeling of all oral-antidiabetic drugs to appropriately reflect the findings of efficacy and safety of these products and to better inform prescribers when selecting an oral anti-diabetic drug for their patients. The following sections of the label should be modified as described below:

1. Under **INDICATIONS and USAGE**
   In the Highlights of Prescribing Information and in the Full Prescribing Information, replace [redacted] (b) (4) with the following sentence:

   "Nesina is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

2. Under Important Limitations of Use
   In the Highlights of Prescribing Information and in the Full Prescribing Information, add a statement listing the major classes of anti-diabetic drugs that have not been studied in combination with your drug, but which are likely to be used in combination with your drug (e.g., sulfonylureas, insulin, etc.).

   "Nesina has not been studied in combination with Drug A."

3. Under **WARNINGS and PRECAUTIONS**
   In the Highlights of Prescribing Information and in the Full Prescribing Information, the following statement should be added to reflect the absence of macrovascular outcome data for all oral anti-diabetic drugs:

   "There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Nesina or any other oral anti-diabetic drug."

4. Under **CLINICAL STUDIES**
   Add a statement at the beginning of this section describing how your drug has been studied.

   "Nesina has been studied as monotherapy and in combination with Drug A, Drug B, and Drug C."

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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/s/

Julie Marchick
3/11/2008 10:48:09 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-271

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

Please refer to your new drug application (NDA) dated December 27, 2008, received December 27, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Nesina (alogliptin) Tablets.

We also refer to your submissions dated February 20 and 22, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **October 27, 2008**.

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

1. Your proposed Prescribing Information recommends a decrease of dose in patients with renal dysfunction, which is based on the results of a small renal pharmacokinetic study. Please submit analyses showing the number of patients with mild (estimated creatinine clearance 50-80 mL/min), moderate (estimated creatinine clearance 30-<50 mL/min), and severe renal impairment (estimated creatinine clearance <30 mL/min) enrolled in each of your phase 3 clinical trials. Please calculate these sample sizes in two ways, one using the Cockcroft-Gault equation and the other using the Modification of Diet in Renal Disease (MDRD) study equation. Please also use these formulas to calculate the number of patients with mild, moderate, and severe renal impairment with ≥6-month and ≥1-year exposures to alogliptin.

2. In the Risk Management Plan section, you mention that you do not believe a formal risk management plan is required. However, you note an "imbalance in reporting rates for angina pectoris and atrial fibrillation" under the *Cardiac events* section of the Risk Management Plan. In addition, in our preliminary review of this application, we note that there is an imbalance in mortality in the clinical program, with 6 deaths in the alogliptin

group and no deaths in the comparator group. At least 5 of the deaths appear to be cardiovascular–related. We will shortly issue an information request for additional analyses of cardiovascular events with alogliptin.

3. From a technical perspective, we note that in some of the case report forms, the links to discrepancy and audit sections are not active.

4. Please provide financial disclosures for investigators with receipt in excess of $25,000 with the actual amounts received.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 12, 2008.

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once review of these requests is complete, we will notify you whether the requested waiver and deferral have been granted.

Please submit your pediatric drug development plan **within 60 days from the date of this letter**. Your pediatric drug development plan must include the following:

- a short description of the planned studies,
- the age groups to be studied,

- the date you plan to start enrollment,
- the date you plan to begin the studies,
- the date you expect to complete the studies, and
- the date you expect to submit the study results.

If you have any questions, call Julie Marchick, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Marchick
3/10/2008 03:05:46 PM
Julie Marchick on behalf of Lina AlJuburi

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-271

NDA ACKNOWLEDGMENT

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nesina (alogliptin) Tablets

Date of Application: December 27, 2007

Date of Receipt: December 27, 2007

Our Reference Number: NDA 22-271

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 25, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, please call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Marchick
1/7/2008 02:57:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,707

Takeda Global Research & Development Center, Inc.
Attention: Christie Ann Idemoto, MS
Program Manager, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015-2235

Dear Ms. Idemoto:

Please refer to your Investigational New Drug Application (IND) file for SYR-322 Tablets.

We also refer to the Pre-NDA meeting between representatives of Takeda Global Research & Development Center, Inc., and the FDA on April 30, 2007.

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) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from Pre-NDA meeting held on April 30, 2007

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 30, 2007
TIME:	10:30 to 11:00 A.M.
LOCATION:	White Oak Campus, Silver Spring, MD
APPLICATION:	IND 69,707
DRUG NAME:	SYR-322 Tablets
TYPE OF MEETING:	Pre-NDA; Type B

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Julie Marchick, M.P.H.

FDA ATTENDEES:

Division of Metabolism and Endocrinology Products:

Mary Parks, M.D.	Director
Eddie Gabry, M.D.	Medical Reviewer
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader
Lina AlJuburi, Pharm.D., M.S.	Regulatory Project Manager
Julie Marchick, M.P.H.	Regulatory Project Manager

Office of Biometrics:

Janice Derr, Ph.D.	Biometrics Reviewer
J. Todd Sahlroot, Ph.D.	Biometrics Team Leader

Office of New Drug Quality Assessment

Stephen Moore, Ph.D.	Product Assessment Leader

Office of Clinical Pharmacology:

Sally Choe, Ph.D.	Clinical Pharmacology Reviewer
Xiaoxiong Jim Wei, Ph.D.	Clinical Pharmacology Acting Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Gregg Redeker	Principal Pharmaceutical Scientist, CMC
Aziz Karim, Ph.D.	Vice President, Clinical Pharmacology
Clare Salamon, M.S.	Principal Toxicologist, Nonclinical Safety and Efficacy
Penny Fleck, M.T.	Senior Program Scientist, Clinical Science
Qais Mekki, M.D., Ph.D.	Vice President, Clinical Science
Barbara Hendrickson, M.D.	Medical Director, Pharmacovigilance
Craig Wilson, Ph.D.	Principal Statistician, Biostatistics
Takayuki Nakano, Ph.D.	Manager, Takeda Pharmaceutical Co. (Japan) Liaison
Mary Jo Pritza, Pharm.D., MPH	Associate Director, Regulatory Affairs
Christie Idemoto, M.S.	Program Manager, Regulatory Affairs

BACKGROUND:

IND 69,707 for SYR-322 was submitted by PPD Development on September 17, 2004. In August 2005, sponsorship of this IND was transferred to Takeda Global Research & Development, Inc. (TGRD). SYR-322 is an orally active dipeptidyl peptidase IV (DPP-IV) inhibitor being studied for the treatment of type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise with or without other antidiabetic therapy. An End-of-Phase 2 Meeting was held on November 28, 2005.

Proposed Indications:

(b) (4)

As an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

(b) (4)

Phase 3 Studies:

SYR-322-PLC-010 "A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with placebo in subjects with type 2 diabetes."

SYR-322-SULF-007 "A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with a sulfonylurea in subjects with type 2 diabetes."

SYR-322-MET-008 "A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with metformin in subjects with type 2 diabetes."

SYR-322-TZD-009 "A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safety of SYR110322 (SYR-322) when used in combination with pioglitazone in subjects with type 2 diabetes."

SYR-322-INS-011 "A multicenter, randomized, double-blind, placebo-controlled study to determine the efficacy and safey to SYR110322 (SYR-322) when used in combination with insulin in subjects with type 2 diabetes."

SYR-322-OLE-12 "A long-term, open-label extension study to investigate the long-term safety of SY110322 (SYR-322) in subjects with type 2 diabetes."

MEETING OBJECTIVES:

- To discuss the content and format of the NDA for SYR-322
- To discuss whether the studies conducted by TGRD are adequate and well-controlled in establishing the safety and effectiveness of TYR-322
- To discuss the planned statistical methods and analyses of the clinical data

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and responses follow in bold.

Chemistry, Manufacturing, and Controls

Question 1:
TGRD plans to submit the SYR-322 marketing application in eNDA format, and therefore will be harmonizing as many of the chemistry, manufacturing, and controls (CMC) modular components as is feasible to support the global registration of the product. Compendial references and product specific information relevant to both the US and European regions will therefore be included in Modules 2.3 and 3.2.P.

Does the FDA agree that inclusion of cross-regional CMC information (e.g., references to ex-US compendia and guidance documents) will not impact the filing of the NDA?

Yes, inclusion of cross-regional CMC information (e.g., references to ex-US compendia and guidance documents) in the NDA is acceptable.

Question 2:
The methods and specifications proposed for the SYR-322 drug substance have been established based on the accumulated history and experience with the starting materials, manufacturing process and controls, and resulting material.

Does the FDA agree that the controls provided demonstrate an adequate level of control for use of the drug substance in a commercial formulation?

Yes, the controls appear adequate for the commercial drug substance. As a comment, we recommend that (b) (4) be identified more specifically in the specification sheet (e.g., (b) (4)). Final determination of the adequacy of the controls will be a NDA review issue.

There is no known toxicity associated with the (b) (4) The impurity has been qualified. The levels of the (b) (4) are hardly detectable in humans.

Question 3:
In anticipation of an approved marketing application, TGRD is pursuing the addition of a second manufacturing site for the SYR-322 drug substance. The change in site will result in several manufacturing changes including equipment used for (b) (4)

(b) (4) the final drug substance. As part of the NDA submission, a comparability protocol developed in accordance with draft FDA Guidance for Industry entitled "Comparability Protocols -- Chemistry Manufacturing, and Controls Information" (February 2003) will be provided encompassing these intended changes and describing the analyses and criteria that will be used to evaluate the suitability of the new processes.

Given a satisfactory current Good Manufacturing Practice status for the facility, does the FDA agree that submission of the proposed comparability protocol and the subsequent associated supplemental results will qualify the indicated changes for approval under the reporting category Change-Being-Effected-in-30-Days?

A reporting category of Changes-Being-Effected (CBE-0) appears appropriate for the proposed changes, provided that the comparability protocol is determined to be scientifically sound.

Question 4:
Methods and specifications have been established to ensure the consistent identity, strength, quality and purity of the SYR-322 drug product.

Does the FDA agree that the proposed controls are appropriate to support the filing and approval of the proposed commercial product?

Yes, the controls appear adequate for the proposed commercial drug product. As a comment, the following should be adequately justified in the NDA: (a) any proposed omission of attribute testing (e.g., degradants, water content, microbial limits) and (b) selection of dissolution conditions and criteria. Final determination of the adequacy of the controls for the drug product will be a NDA review issue.

Question 5:
At the time of the NDA submission, TGRD will provide 12 months of long-term stability data and 6 months of accelerated stability data for the 2 primary tablet strengths of SYR-322 (12.5 mg and 25 mg), both of which are currently being investigated in the phase 3 clinical program. Additionally the application will also include 6 months of long term and accelerated stability for (b) (4) formulations (b) (4) 6.25 mg), which are being developed (b) (4) (b) (4) To support marketing approval of the (b) (4) strengths, TGRD commits to providing 12 month long-term stability results for the (b) (4) 6.25 mg tablets no later than 3 months prior to the Prescription Drug User Fee Act goal date.

Does the FDA agree that this submission strategy is sufficient to successfully file for all (b) (4) strengths of the SYR-322 drug product concurrently?

Yes, the Sponsor's proposal to provide additional stability data for the (b) (4) strengths no later than 3 months prior to the Prescription Drug User Fee Act goal date is acceptable.

Nonclinical

Question 6:
Does the FDA agree that the non clinical program of SYR-322 will adequately support the filing and review of the marketing application?

Yes. The Sponsor has indicated that carcinogenicity and phototoxicity studies are ongoing. The nonclinical summary in your meeting package noted that pre- and postnatal reproductive study in rats and 13-week toxicity study in monkeys have been completed. Submission of complete study reports for those nonclinical studies should be sufficient to support filing and review of your marketing application. The Division expects to receive the outstanding toxicity studies, including the full carcinogenicity study report, prior to or upon submission of the NDA.

Clinical

Question 7:
Does the FDA agree that the pharmacokinetic program and the drug interaction program as outlined in the briefing document will adequately support the marketing application?

Yes, the pharmacokinetic program and the drug interaction program outlined in the briefing document seem to support the marketing application adequately. The Sponsor is asked to provide the validation of multidrug cocktail for Study SYR-322-015 for the lack of interaction among test substrates in future NDA.

Since the multidrug cocktail, which includes fexofenadine, midazolam, dextromethorphan, tolbutamide, and caffeine, is being used for a screening approach, validation is not required if this study will not be used for labeling purposes.

Question 8:
The global phase 3 program was designed to support the following indication statements:

(b) (4)

As an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

(b) (4)

Does the FDA agree that the pivotal phase 3 studies, subject to the review of data, will support the proposed indications?

Yes, the ongoing Phase 3 studies seem adequate to address the proposed indications.

Question 9:
At NDA submission, it is anticipated that a total of over 3000 subjects with T2DM will be exposed to SYR-322, including more than 1000 subjects exposed for 6 months. As TGRD is currently blinded to treatment for the pivotal phase 3 studies, the overall exposure to SYR-322 of individual subjects cannot be accurately determined. However, TGRD estimates the number of subjects exposed to SYR-322 for 1 year will be 370. At the time of the 120-day safety data update, TGRD anticipates 800 subjects exposed to SYR-322 for at least 1 year.

Does the FDA agree that the total and long-term patient safety exposures provided at submission and at the 120-day safety update will adequately support the review and, pending analysis of the overall data package, approval of the marketing application?

The proposed exposure of >1000 patients to SYR-322 for 6 months and >300 patients for 12 months would suffice for NDA filing. More data submitted at the 120-day safety update will be reviewed from the safety perspective as it relates to adequacy of exposure. The Division encourages, and will accept, the submission of data from exposure longer than 12 months at the 120-day safety update.

It is important to remember, however, that complete study reports for claimed indications are expected at the time of NDA submission.

Please present laboratory values for CK values and transaminase levels as follows:

- **% of patients with CK > ULN, > 5x ULN, and 10x ULN. Actual peak values for patients with elevations > 5x ULN should be provided and narratives on patient outcome.**
- **% of patients with ALT or AST > 3x ULN, > 5x ULN, > 10x ULN. Accompanying bilirubin levels should be included and case narratives for patients listed with ALT/AST elevations.**

Question 10:
SYR-322 undergoes very little metabolism and is excreted predominantly as unchanged drug in urine (Section 4.2), therefore a pharmacokinetic study was conducted in subjects with varying degrees of renal impairment [26]. Based upon the results of this study, TGRD is currently developing (b) (4) dose strengths, (b) (4) 6.25 mg, (b) (4) (b) (4)

The data presented in the briefing document support (1) dose proportionality of SYR-322 AUC in healthy subjects [Table 4.e] as well as AUC and Cmax in subjects with T2DM [Table 4.f], and (2) similar systemic exposure to SYR-322 between healthy subjects and subjects with T2DM receiving the same dose (Table 4.d). Therefore, by administering one-half of the anticipated maximum clinical dose for patients with moderate renal impairment and one-quarter of the anticipated maximum clinical dose for patients with severe renal impairment (and ESRD), the plasma concentrations of SYR-322 in patients with T2DM and renal impairment will be similar to those with normal renal function who receive the respective clinical doses of SYR-322.

Also of note, no dose-limiting toxicities or dose-related trends in adverse events were observed in the phase 2 study that evaluated doses of SYR-322 up to 100 mg QD for 12 weeks [Table

6.b,23], which represents a 4-fold higher dose than the anticipated maximum clinical dose of 25 mg.

Does the FDA agree that the approvability of the (b) (4) *strengths of* (b) (4) *6.25 mg is adequately supported by completed clinical studies that have established dose linear kinetics and demonstrated the safety and tolerability of SYR-322 in subjects with T2DM?*

The Division agrees that the approvability of the (b) (4) **strengths of** (b) (4) **6.25 mg,** (b) (4) **would likely be supported by the clinical studies that establish dose linear kinetics and demonstrate the safety and tolerability of SYR-322 in subjects with T2DM.**

Statistics

Question 11:
Does the FDA agree that the study groups (analysis pools) and methods proposed in the draft integrated analysis of safety SAP [Appendix G] are adequate to support the Agency's review of safety data for SYR-322?

Yes. The Sponsor is asked to discuss in the integrated analysis of safety any differences between the pooled safety findings and the safety findings of individual studies.

Question 12:
Does the FDA agree that the planned efficacy data presentation provided in Section 5.2.3 for NDA Section 2.7.3 *Summary of Clinical Efficacy* is appropriate and adequate to support the Agency's review of efficacy data for SYR-322?

Yes. However, the Sponsor is asked to discuss and interpret the similarities and differences in the efficacy results among the Phase 3 studies. It is not necessary to combine or pool the databases of the Phase 3 studies for this discussion. The discussion should be in a separate section of the Summary of Clinical Efficacy.

Question 13:
TGRD plans to provide SAS Version 5 transport files, including pharmacokinetic concentration and parameter data, from the phase 1 studies supporting the marketing application. Each data set will contain case report form raw data. Treatment assignments will be included.

Likewise, TGRD plans to provide SAS Version 5 transport files for all clinical data from phase 2 and 3 studies supporting the submission. Each data set will contain case report form raw data, patient demographic characteristics, treatment assignments, and additional derived variables, as appropriate, as suggested in FDA *Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs (January 1999).*

TGRD will also be providing the Integrated Analysis of Safety data sets in SAS Version 5 transport format for the following domains: exposure, disposition, demographic and other

baseline characteristics, prior and concomitant medications, adverse events, clinical laboratory evaluations, vital signs, and ECGs. The integrated data set files will contain treatment assignments, variables used in the integrated analyses, variables used in the calculations of the analysis variables, variables indicating whether an observation is used in a particular analysis, and other variables as appropriate.

The SAS Version 5 transport files will have a maximum fie size of 100 MB each. Data sets will be separated horizontally (i.e., by record) to meet this fie size limitation.

In accordance with FDA guidance (January 1999), each data set will be accompanied by a data definition table (*define.pdf)*, which will include metadata information, such as variable name, a description of the variable, the type of the variable (numeric, character, date, time) and codes (and decodes). The data definition table will also include a comments field that will provide the method for calculating the derived variables, and the location of raw variables on the respective annotated CRF. A representative data definition table is provided in Appendix H.

Does the FDA agree that the planned content, electronic format, and file size of the transport files and datasets are acceptable?

The Sponsor is asked to submit the following data and datasets to support the population pharmacokinetic analysis of SYR-322:

- **All NONMEM datasets used for model development and validation in SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been *excluded from the analysis* should be maintained in the datasets.**

- **NONMEM control streams and output files should be provided in ASCII (*.txt) format for all major model building steps, e.g., base structural model, covariates models, final model, and validation model.**

- **A model development decision tree and/or table which gives an overview of modeling steps.**

For the population pharmacokinetic report we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

The Division also requests that the analysis files for each Phase 3 clinical study include the derived data file(s) that have the key variables in their final format for use in the statistical analysis of the primary efficacy endpoint.

Question 14:

(b) (4)

The Sponsor must submit patient profiles for Phase 2 and Phase 3 subjects who die, experience serious adverse events, or discontinue use due to adverse events.

Patient profiles may be submitted in .pdf format. The Sponsor may submit an example patient profile to the Division prior to submission of the NDA.

Administrative/Regulatory

Question 15:
Can the FDA please confirm that a deferral of the requirement for pediatric studies as agreed to during the End-of-Phase 2 Meeting is acceptable?

The Sponsor is asked to address plans for pediatric studies at the time of NDA submission.

Question 16:
Per 21 CFR §312.10(a), will the FDA agree to waive the IND annual report in December 2007, since submission of the NDA for SYR-322 will occur in the same month?

Yes.

Question 17:
Does the FDA expect to refer this submission to the Endocrinologic & Metabolic Drug Advisory Committee as part of the review and approval process?

This question cannot be addressed prior to receiving the initial NDA submission.

OTHER COMMENTS:

- If the Sponsor believes that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- The most recent publicly available information on CDER's views on RiskMAPs is available in the following Guidance documents:
    - Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

- Development and Use of Risk Minimization Action Plans:
  http://www.fda.gov/cder/guidance/6358fnl.htm>
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
  http://www.fda.gov/cder/guidance/6359OCC.htm

- If there is any information on product medication errors from the premarketing clinical experience, please submit this information with the NDA application.

- The Sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Minutes Preparer: Julie Marchick
Chair Concurrence: Mary Parks

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

/s/

Julie Marchick
5/11/2007 12:23:00 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,707

PPD Development, LP
Attention: Charity Schuller, Pharm.D., RAC
Manager, Regulatory Affairs
1400 Perimeter Park Drive
Morrisville, NC 27560

Dear Dr. Schuller:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SYR-322 Tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 28, 2005. The purpose of the meeting was to discuss the SYR-322 development program preparation for Phase 3.

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) 796-1168.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Phase 2 meeting minutes from meeting held on November 28, 2005

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 28, 2005
TIME:	2:00 to 3:00 pm
LOCATION:	White Oak Campus, Building 22
APPLICATION:	IND 69,707
DRUG NAME:	SYR-322 Tablets
TYPE OF MEETING:	Type B; End-of-Phase 2

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, M.D.	Director, Office of New Drugs II
David Orloff, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Mary Parks, M.D.	Deputy Director, DMEP
Karen Mahoney, M.D.	Diabetes Clinical Team Leader
Eddie Gabry, M.D.	Clinical Reviewer
Jeri El Hage, Ph.D	Pharmacology/Toxicology Team Leader
Todd Bourcier, Ph.D.	Pharmacology/Toxicology Reviewer
Hae-Young Ahn, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
Jim Wei, Ph.D.	Clinical Pharmacology and Biopharmaceutics Team Leader
J. Todd Sahlroot, Ph.D.	Biometrics Team Leader
Janice Derr, Ph.D.	Biometric Reviewer
Xavier Ysern, Ph.D.	Chemistry, Manufacturing, and Controls Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Takeda Global Research & Development Center, Inc.

Qais Mekki, M.D., Ph.D.	Vice President, Clinical Research (TGRD)
Penny Fleck, MT	Program Manager, Clinical Research (TGRD)
Paul Covington, M.D.	Executive Vice President (PPD)
Aziz Karim, Ph.D.	Vice President, Clinical Research, Pharmacokinetics (TGRD)
Ronald Christopher, Ph.D.	Senior Director, Development (Takeda San Diego)
Clare Salamon, M.S.	Senior Toxicologist (TGRD)
Gregg Redeker	Analytical Chemist (TGRD)
Michelle Usher	Director, Regulatory Affairs, CMC (PPD)
Craig Wilson, Ph.D.	Project Statistician (TGRD)
Takayuki Nakano, Ph.D.	Assistant Manager, Project Coordination (Takeda Japan)
Mary Jo Pritza, Pharm.D.	Senior Manager, Regulatory Affairs (TGRD)
Christie Wong, M.S.	Program Manager, Regulatory Affairs (TGRD)

BACKGROUND:

IND 69,707 for SYR-322 was submitted by PPD Development on September 17, 2004. In August 2005, sponsorship of this IND was transferred to Takeda Global Research & Development, Inc. (TGRD). SYR-322 is an orally active dipeptidyl peptidase IV (DPP-IV) inhibitor being studied for the treatment of type 2 diabetes as an adjunct to diet and exercise with or without other antidiabetic therapy. The proposed Phase 3 program includes 5 clinical studies designed to assess the efficacy and safety of SYR-322 for the treatment of type 2 diabetes mellitus, either as a monotherapy adjunct to diet and exercise or in combination with other antidiabetic medication. A sixth long-term, open-label, extension study will be conducted in subjects with type 2 diabetes mellitus to evaluate the safety of SYR-322 when administered alone or in combination with a sulfonylurea, metformin, a TZD, or insulin.

Proposed Phase 3 Clinical Program

Study SYR-322-SULF-007: *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with a Sulfonylurea in Subjects with Type 2 Diabetes*

Study SYR-322-MET-008: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Metformin in Subjects with Type 2 Diabetes

Study SYR-322-TZD-009: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Pioglitazone in Subjects with Type 2 Diabetes

Study SYR-322-PLC-010: *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Placebo in Subjects with Type 2 Diabetes*

Study SYR-322-INS-011: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of SYR110322 (SYR-322) When Used in Combination with Insulin in Subjects with Type 2 Diabetes

Study SYR-322-INS-012: A Long-Term, Open-Label Extension Study to Investigate the Long-Term Safety of SYR110322 (SYR-322) in Subjects with Type 2 Diabetes

This End-of-Phase 2 meeting was requested on September 30, 2005 (serial # 034). The meeting briefing document was submitted on October 31, 2005 (serial # 036). Additional Nonclinical questions were submitted on November 17, 2005 (serial #037).

MEETING OBJECTIVES:

To discuss the SYR-322 development program in preparation for Phase 3 and ultimately NDA submission.

DISCUSSION POINTS:

CHEMISTRY, MANUFACTURING, AND CONTROLS QUESTIONS

Question 1

The current chemical synthesis used to manufacture the SYR-322 drug substance for phase 3 clinical studies starts with (b) (4) (b) (4) For the manufacture of future batches of SYR-322 drug substance, (b) (4) (b) (4) It is anticipated that the controls detailed in Appendix A of this briefing document will be implemented, and that the prospective sources will be both independently reproducible and consistent across suppliers.

Based on the justification provided in Appendix A, does the Agency concur that the designation of (b) (4) (b) (4) *in the production of SYR-322 is acceptable?*

Yes, this appears to be acceptable.

Question 2

Changes are anticipated between the formulation being supplied for the phase 3 studies as summarized in Section 3.2 and the formulation to be used in future manufacture of SYR-322 tablets. These changes are likely to include the following: (b) (4) (b) (4) Contingent on SYR-322 meeting requirements for (b) (4), TGRD intends to support these changes by submitting documentation consistent with the FDA SUPAC IR Guidance for Industry (November 1995) Section III.B.2a, and Section III.B.2b:Case A.

TGRD plans to submit the NDA with data obtained using the proposal described above. Does the Agency agree that this approach will be sufficient to permit filing and approval of the marketing application?

This approach appears to be acceptable. Keep in mind that if these changes are not deemed minor, the sponsor must demonstrate that Phase 3 and Commercial formulations are bioequivalent.

Question 3

The current test methods and specifications applied to the release of the drug substance and the drug product for use in the phase 3 program are subject to change for the registration and commercial batches of SYR-322. Based on historical data collected and current manufacturing capabilities, the specifications intended for use for the SYR-322 benzoate drug substance and SYR-322 tablets, are provided in Table 3.d and 3.j, respectively.

Does the agency concur that the specifications presented in the briefing document for future manufacturing are sufficient and appropriate to ensure reproducibility and consistency of both the drug substance and drug product?

The submitted specifications are adequate at this stage of drug development. The requirement for bioequivalence will be determined at a later stage.

NONCLINICAL QUESTIONS

Question 1

The completed and ongoing studies that comprise the nonclinical program for SYR-322 are summarized in Table 4.a and Table 4.b, respectively.

Does the Agency concur that current battery of nonclinical studies is sufficient to support NDA filing and product approval?

The battery of nonclinical studies described in Tables 4.a and 4.b, plus the recommended 3 month oral toxicity study in monkeys, appear adequate to support NDA filing. Approval is dependent upon the results of the planned studies.

The sponsor will submit data to address chiral inversion with SYR-322.

CLINICAL QUESTIONS

Question 1

The efficacy of SYR-322 has been demonstrated in a phase 2, double-blind, randomized, 12-week dose-ranging study, SYR-322-003. This study evaluated the safety and efficacy of SYR-322 6.25, 12.5, 25, 50, and 100 mg QD compared with placebo in subjects who were either treatment naive or had inadequate glycemic control on a sulfonylurea, metformin, or a combination of sulfonylurea and metformin. Based on the efficacy results of this phase 2 study, the clinical safety and tolerability of SYR-322 at doses up to 100 mg for 12 weeks, and the adequate nonclinical safety profile, the sponsor has selected the 25 and 50 mg QD regimens for the phase 3 program.

Does the Agency agree that SYR-322 25 mg and 50 mg QD regimens proposed for use in the phase 3 program are justified based on the available nonclinical and clinical data provided in this briefing document?

The rationale for this dose selection is based on the results of one 12 week Phase 2, double-blind, randomized, multicenter, placebo-controlled, parallel-group study of SYR-322 6.25, 12.5, 25, 50, and 100 mg QD. The results of this study do not show any dose response beyond the dose of 25 mg QD. In regard to the primary endpoint, HbA1c, and one of the secondary endpoints, fructosamine, the data support the doses of 12.5 and 25 mg QD. It is only the secondary endpoint of FPG that suggests that the 50 mg dose is more efficacious than the 12.5 mg dose, and even then, the change in FPG obtained with the 50 mg dose is numerically lower than that seen with the 25 mg dose.

From Tables 6.d and 6.f of the briefing document:

	12.5 mg (N=42)	25 mg (N=45)	50 mg (N=43)
HbA1c	**-0.52* (0.174)**	**-0.55* (0.170)**	**-0.42* (0.176)**
Fructosamine	**-17.5* (8.48)**	**-24.1* (8.26)**	**-20.1* (8.73)**
FPG, mg/dL	**-13.6 (9.09)**	**-35.5* (8.88)**	**-24.6* (9.20)**

Therefore, FDA recommends any one or combination of the following options:

1) **To conduct another dose finding study of 16 to 20 weeks duration to evaluate the efficacy of SYR-322 doses ranging from 12.5 to 50 mg QD on HbA1c, as the primary efficacy endpoint.**

2) **To pursue the currently designed, two treatment arms, phase 3 studies using the doses of 12.5 and 25 mg QD instead of 25 and 50 mg QD.**

3) **To add another 12.5 mg QD treatment arm to the currently designed phase 3 studies.**

4) **To start with the monotherapy phase 3 study using 3 treatment arms corresponding to SYR-322 doses of 12.5, 25 and 50 mg QD. Then to choose the most appropriate doses for the add-on studies based on the results of the monotherapy study.**

Question 2

SYR-322 is being developed to improve glycemic control in patients with type 2 diabetes mellitus as described below:

(b) (4)

The phase 3 protocols (submitted on 6 September, 2005 to IND 69,707 [SN:031]) are provided in Appendix B. The designs and target enrollment for these studies are summarized in Section 9.0 and in Table 11.a below.

Table 11.a Proposed SYR-322 Phase 3 Studies

Study Number (a)	Treatment Duration	Study Population/ Dose	Primary Endpoint	Target Enrollment		
					SYR-322	
				Placebo	25 mg	50 mg
SYR-322-SULF-007	6 months	Sulfonylurea add-on study, 25, 50 mg QD	HbA1c	100	200	200
SYR-322-MET-008	6 months	Metformin add-on study, 25, 50 mg QD	HbA1c	100	200	200
SYR-322-TZD-009	6 months	TZD add-on study, 25, 50 mg QD (b)	HbA1c	100	200	200
SYR-322-PLC-010	6 months	Monotherapy, parallel, 25, 50 mg QD	HbA1c	65	130	130
SYR-322- INS-011	6 months	Insulin add-on study, 25, 50 mg QD (c)	HbA1c	100	100	100
SYR-322- OLE-012	See footnote (d)	Open-label, extension study, 50 mg QD	Safety	TBD	TBD	TBD
Targeted Total Exposure				465	830	830

TBD=to be determined.
(a) Studies will be conducted in United States, Canada, Central America, South America, the Dominican Republic, Europe, Israel, South Africa, New Zealand, Australia, and India.
(b) Study will allow subjects taking metformin or sulfonylurea to remain on metformin or sulfonylurea (but not both) during the treatment period.
(c) Study will allow subjects taking metformin to remain on metformin during the treatment period.
(d) The NDA will include 12-month data for a minimum of 400 subjects with type 2 diabetes mellitus exposed to SYR-322.

Does the FDA concur that the proposed phase 3 studies are sufficient to support product approval for the proposed indication?

Except for the lack of a compelling evidence to support the 50 mg dose of SYR-322, the phase 3 studies mentioned above seem adequate by design to meet their objectives of supporting the proposed monotherapy and add-on indications for SYR-322. Therefore, it is prudent to evaluate the efficacy of a lower dosage (at least for the monotherapy study) prior to proceeding with the other phase 3 studies. Please refer to the FDA answer to the first clinical question.

In light of the documented occurrence of ulcerative necrotizing skin lesions, which are apparently irreversible, in the digits and tails of animals treated with DPP-IV Inhibitors, the Division has recently requested that all sponsors of DPP-IV Inhibitors conduct a 3-month toxicity study in monkeys to assess whether the drug causes such lesions at exposures comparable to the proposed clinical doses (or at higher exposures). The 3-month monkey study is not necessary prior to beginning phase 3 studies. However, close attention to the clinical examination of the skin and digits (for discoloration, swelling, atrophy,

ulceration, etc.) is highly recommended at each visit during the phase 3 clinical study. Particular attention should be given to patients with diabetic foot or peripheral arterial disease.

Question 3

As discussed during the pre-IND meeting held on July 20, 2004 (see Appendix D for official FDA pre-IND meeting minutes), the Agency recommended that at least 400 patients be exposed to SYR-322 for 1 year. At NDA submission, it is anticipated that a total of 2110 subjects (218 subjects in phase 2; 1892 subjects in phase 3) with type 2 diabetes mellitus will be exposed to SYR-322, including more than 1000 subjects exposed for 6 months, and at least 400 subjects exposed for 1 year.

Does the Agency agree that the total patient exposures to SYR-322 are adequate to support NDA filing and product approval?

Yes, the Agency agrees that the proposed total patient exposures to SYR-322 would be adequate to support NDA filing.

Question 4

The proposed statistical analysis plan for the SYR-322 phase 3 program is summarized in Section 10.0 of this briefing document.

Does the Agency concur that the proposed primary analysis methodology for the phase 3 pivotal studies is sufficient to support the proposed indication?

A. **Analysis population: It is acceptable to use the full analysis set (FAS) in the primary analysis, where the FAS consists of all subjects who have a baseline assessment and at least one post-baseline assessment of the response variable.**

B. **The use of the last observation carried forward (LOCF) method for imputing the primary efficacy endpoint in patients who drop out before week 26 in the full analysis set for the primary efficacy analysis is acceptable.**

C. **Concerning the primary analysis of covariance (ANCOVA) model: The Division recommends that the ANCOVA model be completely pre-specified, including the covariates to be included in the model, prior to the start of the study. The Division does not agree with** (b) (4) (b) (4) **The sponsor should have sufficient information at this stage of clinical development of the compound to identify variables that are good candidates for inclusion in the model, i.e., covariates expected to be at least moderately correlated with the response. The Division would like to discourage the practice of blinded data review since it is unclear how to assess the effect of changing statistical models on Type 1 error after seeing blinded data.**

D. **The sequence of statistical tests proposed for comparing the treatment groups in the primary efficacy evaluation: The Division agrees that the proposed step-down approach will provide strong control of Type I error, i.e.: the first step is to evaluate the 50 mg dose group vs. the 0 dose group at a 2-tailed α of 0.05, and then conditional on the statistical significance of the first step, the second step is to evaluate the 25 mg dose group vs. the 0 dose group. Please refer to the following points of clarification:**

a) **The test in the second step, comparing the 25 mg dose group vs. the 0 dose group, is evaluated at a 2-tailed α of 0.05.**
b) **The protocol notes that these tests are 2-sided *t*-tests, and we would like to clarify that these *t*-tests are constructed from linear contrasts of effects that are estimated from the Model I ANCOVA.**

E. **The Division recommends that the protocols include plans for a sensitivity analysis of the primary efficacy endpoint. The Division suggests that a sensitivity analysis can include an analysis by subgroups of patients, with the subgroups defined by length of retention in the study. A useful way of defining subgroups may be to use the time frames proposed for the rescue criteria for hyperglycemia:**
   a) **Patients who dropped out after more than 1 week of treatment but prior to the week 4 visit;**
   b) **Patients who dropped out after the week 4 visit but prior to the week 8 visit;**
   c) **Patients who dropped out after the week 8 visit but prior to the week 12 visit;**
   d) **Patients who dropped out after the week 12 visit but prior to the week 26 visit;**
   e) **Patients who completed the study.**

F. **The Division agrees with the proposed method for exploring the treatment by region interaction and treatment by baseline interactions (the ANCOVA "Model 2" as described in the protocols)**

G. **The Division agrees with the proposed additional exploratory analysis to explore heterogeneity of response by baseline levels of previous diabetic therapy, duration of diabetes, and in pre-specified subsets of the patient population, including the ANCOVA "Model 3" as described in the protocols. The Division suggests that a further exploratory analysis of the primary efficacy outcome can include alternative methods of accounting for patients who required hyperglycemic rescue therapy. A useful reference to these methods is White et al., *Statistics in Medicine*, 2001, 20: 2995-3008 ("Randomized clinical trials with added rescue medication: some approaches to their analysis and interpretation").**

Question 5

The additional planned pharmacokinetic studies for completion of the SYR-322 phase 1 clinical program are summarized in Section 5.3.

Does the Agency concur that these planned phase 1 studies are sufficient to support NDA filing and product approval?

The planned Phase 1 pharmacokinetic drug interaction studies are acceptable. However, since the SYR-322 is mainly excreted unchanged through the kidney, the Division would like to suggest a transporter-based drug interaction study with cyclosporine to investigate the effect of cyclosporine on pharmacokinetics of SYR-322.

REGULATORY QUESTIONS

Question 1

The sponsor recommends that a thorough review of the safety and efficacy data derived from the adult population in the phase 3 clinical program be conducted prior to administering SYR-322 to children with type 2 diabetes mellitus. Consequently, the sponsor is requesting a formal deferral of the requirement to conduct pediatric studies as permitted under 21CFR 314.55 (b)(1) until after approval of SYR-322 in the adult population.

Does the Agency agree to grant a deferral for initiation of formal pediatric clinical studies until SYR-322 is approved for use in the adult population?

The Division agrees that pediatric studies should not be initiated until the safety profile of SYR-322 is characterized in adults. Therefore, the sponsor's request for a deferral of pediatric studies will be granted.

Responses to Additional Questions submitted on November 17, 2005 (serial # 037):

1. Can the Agency clarify if these findings are observed with DPP-4 inhibitors known to be covalent or non-covalent receptor bound molecules?

   Necrotic skin lesions have been observed with both types of molecules.

2. Can the Agency provide information about the shortest latency period for the onset of this finding?

   Lesions can be observed within 1-2 weeks at high doses. The lesions are both dose and duration dependent.

3. Can the Agency provide guidance regarding the strain of monkey to use in the repeat dose toxicity study?

   Lesions have been observed primarily in cynomolgus monkey, but have also been seen in rhesus.

4. Can the Agency provide information regarding the exposure multiples for these necrotic skin lesions relative to the human exposure based on AUC estimates?

   The lesions appear early at doses with safety margins but are seen with progressively lower doses with increased duration of dosing.

5. Are there exposure multiples at the NOAEL?

   Not always as lesions have been seen at exposures comparable to the therapeutic range by the last two weeks of the 13-week studies.

6. We propose evaluating doses that are 1 and 10-fold the AUC at the highest clinical dose expected for approval. Does the agency agree with this dose level proposal?

   No. We would recommend 3 dose groups at 1, 3 and 10 X clinical AUC exposures at the MRHD. If lesions are observed early at 10 X, later at 3 X, but not at 1X, we would recommend extension of the treatment period for the 1X group to define whether this dose is truly a NOAEL.

7. Are there non-routine clinical pathology biomarkers that should be monitored in the repeat dose studies that could be clinically relevant?

   No, the mechanism involved in this toxicity is not currently understood.

8. Given that these necrotic lesions have only been observed in primates, can the agency comment as to whether this finding might be a species related finding (e.g., due to different metabolic profiles)?

   Related findings have been observed less frequently in dogs (footpad lesions, favoring hind paws, edema) and rats (discoloration/ lesions on ears). There is no evidence for species specific metabolites contributing to the lesions in monkeys.

Minutes preparer: Lina AlJuburi
Chair concurrence: David Orloff

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/s/

Lina Aljuburi
12/28/2005 01:12:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND 69,707

(b) (4) PPD Development
(b) (4)

Dear Ms. Nincehelser:

Please refer to your Pre-Investigational New Drug Application (PIND) file for SYR110322.

We also refer to the meeting between representatives of your firm and the FDA on July 20, 2004. The purpose of the meeting was to discuss the overall development plan for SYR110322.

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, call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of meeting minutes from July 20, 2004 PreIND meeting

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2004
TIME: 3:00 to 4:00 pm
LOCATION: Parklawn Building, Chesapeake Conference Room
APPLICATION: PIND 69,707
DRUG NAME: SYR110322 (b) (4)
TYPE OF MEETING: Type B; PreIND

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Dragos Roman, M.D.	Medical Officer
Jeri El Hage, Ph.D.	Pharmacology/Toxicology Team Leader
Shen Xiao, Ph.D.	Pharmacology/Toxicology Reviewer
Sang Chung, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Xavier Ysern, Ph.D.	Chemistry, Manufacturing, and Controls Reviewer
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Representing PPD Development and Syrrx

Randy Anderson, Ph.D.	Vice President, PPD Development
Ronald Christopher, Ph.D., DABT	Senior Director-Development, Syrrx
Lelia Davenport	Director-Product Development, PPD Development
Gail McIntyre, Ph.D., DABT	Senior Vice President, PPD Discovery
Marc Navre, Ph.D.	Senior Director-Leads Discovery, Syrrx
Melanie Nincehelser, Pharm.D.	Associate Director-Regulatory Affairs, PPD Development
Michelle Usher	Director-Regulatory Affairs, PPD Development
Jeffrey Stafford, Ph.D.	Senior Director, Chemistry Syrrx

Via teleconference

Paul Covington, M.D.	Executive Vice President, PPD Development
Lisa Hornick, M.D.	Associate Medical Director, PPD Development

BACKGROUND:

SYR110322 (b) (4) is a dipeptidyl peptidase IV (DPP-IV) inhibitor. According to the firm, SYR110322 is a potent, selective, orally available inhibitor of DPP-IV which is responsible for degradation and inactivation of glucagon-like peptide 1 (GLP-1) and gastric inhibitory

polypeptide. The proposed indication is for the treatment of type 2 diabetes (b) (4) adjunct to diet and exercise to improve glycemic control (b) (4) (b) (4)

Proposed clinical development program to be conducted under a U.S. IND:

Phase 1

The initial clinical study the firm proposes to conduct is entitled, "A randomized, double-blind, placebo-controlled, single-dose, dose-ascending study of the safety, tolerability, pharmacokinetic and pharmacodynamic effects of SYR10322 in healthy male volunteers." The dosage range is from 25 to 800 mg (or placebo) administered orally.

The first study in subjects with type 2 diabetes the firm proposes to conduct is entitled, "A multicenter, randomized, double-blind, placebo-controlled, repeat-dose study to determine the safety, pharmacokinetic and pharmacodynamic effects, and efficacy of SYR110322 in patients with Type 2 diabetes who are either newly diagnosed or managed with diet and exercise alone for the past 3 months." The dosage range is from 25 to 400 mg (or placebo) administered orally as a once daily dosage.

Phase 2

The firm proposes a proof-of-concept study entitled, "A multicenter, randomized, double-blind, placebo controlled comparison study to determine the efficacy and safety of SYR110322 in patients with Type 2 diabetes who are either receiving no current treatment or currently treated with a sulfonylurea, metformin, or a combination of sulfonylurea and metformin." The dosage range is from 25 to 100 mg (or placebo) administered orally as a once daily dosage.

The firm requested a PreIND meeting on May 24, 2004 and submitted the background package on June 25, 2004.

MEETING OBJECTIVES:

To discuss the overall development plan of SYR110322.

DISCUSSION POINTS:

The firm requested responses to the following questions. The questions are repeated below and the responses are bolded.

Chemistry, Manufacturing and Controls (CMC)

Drug Substance

CMC–Q1: Does the Agency agree with our proposed tests and specifications for the active pharmaceutical ingredient (API)?

The Agency does not have any objection to the proposed drug substance specifications (DS). However, as development of the drug progresses a reevaluation/update of the DS specifications may be needed.

For guidance, the sponsor is referred to: (1) Guidance for Industry "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products" Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) November 1995, which can be found at http://www.fda.gov/cder/guidance/index.htm and (2) Guidance for Industry "INDs for Phase 2 and Phase 3 Studies – Chemistry, Manufacturing, and Controls Information" Center for Drug Evaluation and Research (CDER) May 2003, which can be found at http://www.fda.gov/cder/guidance/index.htm.

CMC-Q2: [redacted] (b) (4) As expected using fundamental chemistry principles, no [redacted] (b) (4) of the API has been observed from preliminary stability studies or forced degradation studies. Does the agency concur with this approach?

[redacted] (b) (4)

Drug Product

CMC–Q3: Does the Agency agree with our proposed tests and specifications for the drug product?

The Division does not have any objection to the proposed drug product specifications. Refer to response to CMC-Q1.

CMC-Q4: At the time of IND submission, we will have no stability data on the clinical batch of drug product. However, the IND will contain the batch analyses of the clinical lot of active ingredient and formulated drug product. Additionally, the IND will contain two-month accelerated stability data from a development batch, similarly produced to what is proposed for the clinical batch, with the only difference being [redacted] (b) (4) Stability of the clinical batch will be monitored concurrently with the clinical program and data will be provided as they become available. Does the Agency agree with this approach.

This appears to be acceptable.

CMC-Q5: The drug product currently exists as a [redacted] (b) (4) formulation. However, there are plans to change the formulation to a tablet prior to the "proof of concept" study tentatively scheduled to begin in March 2005. [redacted] (b) (4) (b) (4) Additionally, preclinical data indicate that the

oral bioavailability in primates and canines with the (b) (4) formulation is 85%, which is predicted to be similar to humans. Also, the objective of the two human studies is to obtain safety data at higher doses than the doses planned for the "proof of concept" trial. Given the above and since the (b) (4) tablet formulations are immediate release, we plan to demonstrate equivalency between these formulations using dissolution data only. Does the Agency agree with this approach?

This approach appears to be acceptable. However, clinical pharmacology and biopharmaceutics studies should be conducted with the tablet formulation.

General

CMC-Q6: Are there any other CMC concerns that will prevent the successful filing of this IND?

The Division does not have any CMC comments or concerns at this time.

Nonclinical Pharmacology (NC)/Toxicology/ADME

NC–Q1: Does the Agency agree that the existing nonclinical safety data and proposed preclinical development plan will support safe use of the drug in the intended clinical studies?

The completed preclinical studies can support a clinical study with durations up to 28 days. The proposed preclinical development plan can support the proposed intended clinical studies. However, we can not determine whether the proposed doses are appropriate until we have reviewed the full reports. In addition, since the highest doses tested in both the rat and dog were defined as the no adverse effect levels, future toxicity studies should evaluate higher doses associated with frank toxicity in order to identify potential target organs.

NC–Q2: To support the clinical program up through PII Proof-of-Concept, the preclinical program includes toxicology studies of 3 months duration and the full genotoxicity panel. Do you agree that the strategy for the preclinical toxicology program (outlined in Section 4, Table 4.30), which we've designed to be consistent with ICH M3, is adequate to support our clinical development program and the NDA submission?

The nonclinical program listed in Table 4.30 is adequate to support the clinical development program and the NDA submission.

NC–Q3: Are there any issues with DPP IV inhibitors that we have not addressed in our preclinical toxicology program?

No, the preclinical toxicology program appears to be acceptable.

Additional Recommendations:

- **Please be advised that an assessment of chiral inversion should be conducted in all species (rat, dog, humans).**
- **Since data suggest SYR110322 is demethylated by CYP 2D6, a clinical drug-drug interaction study with a 2D6 substrate (dextromethorophan) should be conducted to determine the effects on SYR 110322 and 110324 exposures prior to dose selection for the thorough QT study.**

Clinical (C)

General Development Plan

C-Q1: Does the Agency agree that the clinical development plan is complete, and given positive results, will support an NDA?

The general plan and outline of the clinical development plan appear to be acceptable. Whether the currently outlined development plan is complete will depend on the efficacy and, particularly, the safety findings that will be gleaned with further development of SYR110322.

General comments:

- **Characterize the metabolism of SYR110322 in humans since animal data cannot be extrapolated across species. Pay special attention to pharmacologically active metabolites and their kinetics in order to assess if they can have implications for safety (e.g., QT interval prolongation).**
- **During dose selection give consideration to establishing not only a maximally effective dose but also a range of doses (including a minimally effective dose); if the maximally effective dose is not proven safe in Phase 3 clinical trials, lower doses (or different regimens: BID vs. QD) may prove to be safe and effective in the final analysis.**

C-Q2: Does the Agency agree with the proposed primary and secondary efficacy endpoints for the Phase III pivotal studies?

The proposed primary and secondary efficacy endpoints selected for Phase 3 studies appear to be acceptable.

C-Q3: Our Phase III pivotal trials will assess efficacy of the primary endpoint, HbA1c, at 6 months in at least 2 controlled studies. The Phase III pivotal trials will also include controlled studies assessing efficacy of the primary endpoint, HbA1c, at 3 months. Patients from the 3-month and 6-month controlled studies will be able to enroll in an open-label extension study. We will assess continued efficacy on the primary endpoint to 1 year in the open-label extension study. We assume that at least 100 patients will be evaluable for efficacy at 1 year of treatment. Does the Agency agree that this design and the number of patients projected to complete 1 year treatment are sufficient for determination of long-term efficacy?

Comments on Study Design:

- **For a monotherapy indication: the Division agrees with the sponsor's plan to use a randomized, placebo-controlled, dose-ranging trial design.**
- **For a combination therapy indication: the Division agrees with the sponsor's plan to use metformin, a sulfonylurea, and a thiazolidinedione as background medications in individual trials; the randomized, placebo-controlled trial design is acceptable; the "placebo only" arm may not be necessary for the combination indication because the primary efficacy analysis will compare the SYR110322/background medication arm with the placebo/background medication arm.**
- **Whether one or more clinical trials are required for the monotherapy indication will depend on 1) the overall configuration of the Phase 3 clinical program, 2) the magnitude of the treatment effect and how consistent it is across the development program, and 3) the presence (or absence) of safety signals and the size of the safety dataset.**
- **Traditionally, the Division has asked for a minimum of six months of controlled efficacy data in pivotal trials; shorter clinical trials (e.g., 3-4 months), if submitted, were looked at as supportive evidence of efficacy**
- **In the placebo arms, rescue criteria for lack of glycemic improvement should be implemented and should be consistent within the clinical trial and across trials; for patients who meet the predefined rescue criteria, their HbA1c values should be censored at the time of rescue for the purpose of efficacy analyses**
- **Include a comparison (across treatment arms) of the percentage of patients who require rescue therapy as a secondary efficacy endpoint**
- **For insulin clinical trials, insulin dosing should be done in a manner that allows adjustments in accordance with good clinical practice; a control arm is recommended (for such a design see Aviles-Santa L et al. "Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial." Archives of Internal Medicine, 1999, Vol.131, 182-88)**

Post-meeting comments:

With respect to selecting rescue criteria for lack of glycemic improvement on-trial, the Division recommends that such criteria should take into consideration both the absolute fasting plasma glucose (FPG) and the duration of participation in the trial. For example, in a hypothetical subject enrolled with a FPG of 240 (or HbA1c around 10%) a potential set of stopping rules may be the following:

- **a glucose > 270 mg/dl on repeat measurements after one week on trial**
- **a FPG >200 AND < 20 mg/dl fall from baseline at weeks 4-8**
- **FPG > 200 mg/dl at weeks 12-20**
- **HbA1c>8% at weeks 20-26**

This suggested set of rules may be replaced by an analogous one that respects the same basic principles.

Number of patients:

If SYR110322 treatment was to be approved, it will be used long-term since type 2 diabetes is a chronic, lifelong condition. Therefore, the level of patient

exposure required by the Division at the time of registration is in excess of the current ICH guidelines. Since currently there is no approved DPP-IV inhibitor and the safety profile of this new class of compounds is not known and cannot be fully anticipated, collection of extensive and complete safety data information is of particular importance. The Division encourages the sponsor to enroll as many patients in extension-studies in order to collect additional safety data and to have approximately 400-500 patients exposed for one year.

C-Q4: We propose to study SYR110322 in combination with metformin, a thiazolidinedione, or a sulfonylurea in Phase III studies. We have performed a metabolic stability study involving co-incubation of SYR110322 with rosiglitazone, glyburide and glipizide in human liver microsomes and found no effect of SYR110322 on the metabolism of the other co-incubated drugs, nor was there an effect of the co-incubated drugs on the metabolism of SYR110322. (Please refer to Section 4 of this document for a summary of this study) A similar study will be conducted to evaluate potential effects on metabolism following co-incubation of SYR110322 with metformin. Based on the lack of effect on metabolic stability in this *in vitro* study, we propose to go directly into the Phase III studies, and collect *in vivo* drug-drug interaction data in the context of these studies. Does the Agency agree with this approach?

The Division agrees that Phase 3 studies can be initiated without a controlled *in vivo* drug-drug interaction study based on preliminary metabolic stability results from *in vitro* studies and proper monitoring. However, the sponsor would need to characterize metabolism of SYR110322 further for labeling, specifically, 1) identification of responsible metabolic isozymes using standardized *in vitro* studies and 2) conduct an *in vivo* drug-drug interaction study based on results of *in vitro* metabolism studies or clinical relevance. In addition, evaluation of a drug-drug interaction between SYR110322 and metformin is recommended. Metformin is primarily eliminated through active secretion in the renal tubule, and therefore, there is a potential drug-drug interaction through the renal elimination pathway.

C-Q5: (b) (4) (b) (4) Is the Agency in agreement that this would be sufficient for an overall safety database for the drug product?

No, refer to response to C-Q3.

C-Q6: Is the Agency aware at this time of any clinical issues, in reference to DPP IV inhibitors, that we have not addressed in our clinical program and that may be relevant to on-going development of this compound?

Not at this time.

C-Q7: We propose to conduct a single-dose, placebo/active-controlled, crossover Phase I study evaluating potential effects of a dose of SYR110322 that is 4- to 8-fold greater than the targeted efficacious dose on the QT interval. This study will be conducted prior to Phase III. Does the Agency agree with the proposed dosing of this study?

The Division recommends a definitive QT prolongation study using a suprapharmacological dose of SYR110322 against placebo and positive controls. ECG data should be collected at time of anticipated maximum serum concentration for SYR110322. The sponsor should refer to the concept paper on QT prolongation, entitled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs" (http://www.fda.gov/cder/calendar/meeting/qt4jam.pdf). The sponsor has made dose calculations based on a simple extrapolation. The sponsor should take into consideration doses with clinical relevance in a thorough QT study. For example, doses should cover exposure change in a potential drug-drug interaction or in a special situation (i.e., exposure change in a poor metabolizer for 2D6 substrate with a patient with moderate renal impairment.)

Questions about the Phase I Study in Healthy Volunteers

The first study proposed under the IND will be a double-blind, placebo-controlled, sequential, single-dose, dose-ascending, study of the safety, tolerability, pharmacokinetic and pharmacodynamic effects of SYR110322 in healthy male volunteers. An overview of this study, as well as the protocol synopsis is included in Section 5 of this document. With regard to this study, we wish to discuss the following questions:

C-Q8: Does the Agency agree with the design of the Phase I study and in particular does the Agency agree with:

a) The selection of doses based on the rationale provided?

The selected doses (25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg) appear to be acceptable. The Division needs to evaluate the animal toxicology data to determine if the proposed no observed effect level (NOEL) is acceptable.

b) The intent to investigate a maximum dose that represents a dose well above the lowest dose required to inhibit DPP IV by 80%, but still less than half the human equivalent dose of the NOAEL in the 28 day canine study?

The proposed approach appears to be acceptable.

c) The safety assessments in the study?

The safety assessments appear to be acceptable.

d) The pharmacodynamic assessments in the study?

The pharmacodynamic assessments appear to be acceptable. The Division understands from the sponsor that a reliable GLP-1 assay may not be available for the Phase I studies. Information from other pharmacodynamic evaluations may be analyzed instead and, ultimately, it is the effect on glycemic control of SYR110322 in clinical trials and a favorable safety profile that will support potential registration.

Questions about the Repeat-Dose Study in Patients with Type 2 Diabetes Mellitus
The second study proposed to be conducted under the IND will be a repeat-dose, multicenter, double-blind, placebo-controlled, study of the safety, pharmacokinetic and pharmacodynamic effects of SYR110322 in patients with type 2 diabetes mellitus who are either newly diagnosed or managed with diet and exercise alone for the past 3 months. This study will incorporate a standard meal challenge to assess the effect of food on plasma glucose and insulin. An overview of this study, as well as the protocol synopsis is included in Section 5 of this document. With regard to this study, we wish to discuss the following questions:

C-Q9: Does the Agency agree with the design of the repeat dose study described above and in particular does the Agency agree with:
a) The selection of doses based on the rationale provided?

The selected doses (25 mg, 100 mg, 400 mg) appear acceptable assuming that they are well tolerated in the single-dose study and supported by animal toxicology data.

b) The safety assessments in the study?

The safety assessments appear to be acceptable.

c) The pharmacodynamic assessments in the study?

The pharmacodynamic assessments appear to be acceptable.

Questions about the Phase II Study in Patients with Type 2 Diabetes Mellitus
A multicenter, double-blind placebo-controlled comparison study will be conducted in patients with type 2 diabetes mellitus who are receiving no antidiabetic therapy for at least 3 months (ie, either newly diagnosed or experiencing inadequate glycemic control with diet and exercise for at least 3 months prior to screening) or are currently treated with a sulfonylurea, metformin, or a combination of the two. All eligible patients will undergo a 2-week washout prior to randomization along with dietary coaching and home glucose monitoring training. The objectives of the study are: 1) to determine the overall glycemic control of SYR110322 after 4, 8, and 12 weeks of treatment as determined by HbA1c, fasting plasma glucose and fructosamine; and 2) to determine the safety of SYR110322 by evaluating adverse events, clinical laboratory parameters, ECGs, physical examinations and hypoglycemic events. An overview of this study, as well as the protocol synopsis is included in Section 5 of this document. With regard to this study, we wish to discuss the following questions:

C-Q10: Does the Agency agree with the design of the Phase II study and in particular does the Agency agree with:
a) The composition of the study population in the study?

The proposed combination of naïve and non-naïve patients with type 2 diabetes appears to be acceptable.

b) The efficacy assessments in study?

The proposed efficacy assessments appear to be acceptable.

ACTION ITEMS:

The sponsor plans to submit the initial IND submission in September 2004.

Minutes Preparer: Lina AlJuburi

Chair Concurrence: David Orloff

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/s/

Lina Aljuburi
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