

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206073Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206073

SUPPL # N/A

HFD # N/A

Trade Name Glyxambi

Generic Name empagliflozin and linagliptin

Applicant Name Boehringer Ingelheim

Approval Date, If Known January 30, 2015

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?

3

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).

N/A

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# 201280	Linagliptin tablets
NDA# 201281	Linagliptin/metformin HCl tablets
NDA# 204629	Empagliflozin tablets

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:

N/A

(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:

N/A

- (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:

1275.1 - A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control

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

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

N/A

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

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

N/A

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"):

1275.1 - A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control

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 # 108388	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		!

(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:

N/A

Name of person completing form: Callie Cappel-Lynch
Title: Regulatory Project Manager
Date: 1/20/2015

Name of Office/Division Director signing form: William Chong (on behalf of Jean-Marc Guettier)
Title: Clinical Team Leader, Acting

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/

CALLIE C CAPPEL-LYNCH
01/20/2015

WILLIAM H CHONG
01/20/2015
Signing on behalf of Dr. Jean-Marc Guettier

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 206073	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Glyxambi Established/Proper Name: empagliflozin and linagliptin Dosage Form: tablets		Applicant: Boehringer Ingelheim Agent for Applicant (if applicable): N/A
RPM: Callie Cappel-Lynch		Division: Metabolism and Endocrinology Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
• Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is January 30, 2015 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (specify type and date for each action taken) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1 <i>(confirm chemical classification at time of approval)</i>	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation	
NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies	
<input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required	
Comments: None	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
• Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) AP January 30, 2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (indicate date(s))	May 9, 2014
• Review(s) (indicate date(s))	May 7, 2014
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> None DMEPA: June 16 and 19, 2014 DMPP/PLT (DRISK): January 8, 2015 OPDP: January 7, 2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	March 27, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>December 3, 2014</u> If PeRC review not necessary, explain: 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	January 27, 2015 January 14, 2015 December 8, 2014 October 10, 2014 August 27, 2014 July 10, 2014 June 10, 2014 June 4, 2014 April 11, 2014 April 8, 2014 March 31, 2014 March 27, 2014 February 11, 2014
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	November 19, 2014 - PeRC template September 11, 2014 - memo of OSI tcon
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A or no mtg Meeting cancelled at sponsor request, letter included- preliminary comments sent 7/29/13 also included. July 28, 2010 July 9, 2014 October 30, 2014 N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None See CDTL Review dated January 29, 2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	January 29, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (indicate date for each review) 	See CDTL review for final review March 27, 2014
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (indicate date for each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo) 	See CDTL review dated January 29, 2015 (pg. 139-140)
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) REMS Memo(s) and letter(s) (indicate date(s)) Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	N/A N/A January 2, 2015
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) 	October 29, 2014 October 28, 2014 October 24, 2014 (2) October 15, 2014 October 6, 2014
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> › Clinical Microbiology Team Leader Review(s) (indicate date for each review) 	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	October 15, 2014 March 28, 2014
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	October 7, 2014 April 8, 2014
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) 	October 3, 2014 April 11, 2014

Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)		October 13, 2014
• Pharm/tox review(s) including referenced IND reviews (indicate date for each review)		October 12, 2014 March 27, 2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		October 15, 2014 September 16, 2014 August 19, 2014 March 20, 2014 March 19, 2014
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		August 8, 2014 February 25, 2014
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)		See product quality review dated 8/19/14 (pg. 67-68)
<input type="checkbox"/> Review & FONSI (indicate date of review)		
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁵)		Date completed: July 22, 2014 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)		N/A

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

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review dated 8/19/14 pg. 6)

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	N/A
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the "preferred" name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

From: CappelLynch, Callie
To: ["chung.lee-sogaard@boehringer-ingenlheim.com"](mailto:chung.lee-sogaard@boehringer-ingenlheim.com)
Subject: RE: NDA 206073 empagliflozin + linagliptin FDC
Date: Tuesday, January 27, 2015 4:46:00 PM
Attachments: [Empagliflozin_Linagliptin_US_PI_FDA_Comments_1.27.15.docx](#)
[image001.png](#)

Hi Chung,

Please see the attached PI for NDA 206073 with FDA comments. If you have any questions, please contact me ASAP. We request that you review our comments and provide revised labeling by COB tomorrow, Wednesday, January 28, 2015.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingenlheim.com [mailto:chung.lee-sogaard@boehringer-ingenlheim.com]
Sent: Tuesday, January 27, 2015 10:21 AM
To: CappelLynch, Callie
Subject: RE: NDA 206073 empagliflozin + linagliptin FDC

Dear Callie,

Thanks again. As you can imagine, we are looking forward to the next round of comments!

Chung.

Chung Lee-Sogaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingenlheim.com

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, January 27, 2015 10:16 AM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Subject: RE: NDA 206073 empagliflozin + linagliptin FDC

Hi Chung,

I hope to have labeling to you at some point today. If this changes, I'll let you know. As stated before, senior management has been involved in this review. At this time, I do not believe we have any comment on the most recent carton/container labels.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingenlheim.com [<mailto:chung.lee-sogaard@boehringer-ingenlheim.com>]
Sent: Friday, January 23, 2015 8:14 AM
To: CappelLynch, Callie
Subject: NDA 206073 empagliflozin + linagliptin FDC

Dear Callie,

I was wondering if there might be any update regarding review of the draft labeling. It would be really helpful to have an idea approximately when we can expect the next round of comments and whether senior management will be involved in the review. Also, would you have any update regarding carton and container labeling?

Thank you in advance.
Chung.



Chung Lee-Søgaard, Ph.D.

Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 798 4224 :: C: (b) (6)
chung.lee-sogaard@boehringer-ingenlheim.com



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/s/

CALLIE C CAPPEL-LYNCH
01/27/2015

From: CappelLynch, Callie
To: ["chung.lee-sogaard@boehringer-ingenlheim.com"](mailto:chung.lee-sogaard@boehringer-ingenlheim.com)
Subject: RE: NDA 206073 Labeling Comments
Date: Wednesday, January 14, 2015 5:54:00 PM
Attachments: [Empagliflozin_Linagliptin_US_PI_BI_Response_to_FDA_17DEC2014_\(3\).docx](#)

Hi Chung,

Please see the attached label with FDA comments. Please review and provide revised labeling by COB Monday January 19, 2015. If you have any questions, please contact me.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingenlheim.com [mailto:chung.lee-sogaard@boehringer-ingenlheim.com]
Sent: Tuesday, January 13, 2015 3:47 PM
To: CappelLynch, Callie
Subject: RE: NDA 206073 Labeling Comments

Dear Callie

I was wondering if we can still expect labeling comments back this week?

Thank you!
Chung.

Chung Lee-Søgaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingenlheim.com

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, January 05, 2015 2:42 PM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Subject: RE: NDA 206073 Labeling Comments

Hi Chung,

I hope you enjoyed your holiday as well. I'm aiming to send comments by early next week. If this changes, I'll let you know.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingenlheim.com [mailto:chung.lee-sogaard@boehringer-ingenlheim.com]

ingelheim.com]

Sent: Monday, January 05, 2015 2:33 PM
To: CappellLynch, Callie
Subject: RE: NDA 206073 Labeling Comments

Dear Callie,

I hope you had a very good holiday and a great start to 2015.

I was wondering if it would be possible to find out approximately when we could expect the next round of labeling comments.

Thank you!
Chung.

Chung Lee-Sogaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingelheim.com

From: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Sent: Wednesday, December 17, 2014 10:56 AM
To: 'CappellLynch, Callie'
Subject: RE: NDA 206073 Labeling Comments

Dear Callie,

Please find attached our response to FDA labeling comments received on December 8, 2014 for the empa + lina FDC tablets (NDA 206073). BI has accepted FDA suggested revisions and has marked proposed changes in track change mode. Those revisions requested in a comment bubble, but which were not made directly in the labeling by FDA, were kept in track change mode.

Since there have been limited review issues and it now appears that there are few remaining open issues to the draft labeling text, do you think there is any possibility that FDA might take action on this NDA prior to target PDUFA action date of January 30, 2015? Any insights you can provide on this would be most appreciated.

Please let me know if you have any questions.

Best regards,
Chung.

Chung Lee-Sogaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262

Email: chung.lee-sogaard@boehringer-ingelheim.com

From: CappelLynch, Callie [<mailto:Callie.CappelLynch@fda.hhs.gov>]
Sent: Monday, December 08, 2014 12:41 PM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Subject: NDA 206073 Labeling Comments

Hi Chung,

Please see the attached PI for NDA 206073 with FDA comments. If you have any questions, please let me know. Please respond to these comments by COB December 17, 2014.

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 you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change or COMPANY comment."

Thanks,

Callie Cappel-Lynch
Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-8436

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/s/

CALLIE C CAPPEL-LYNCH
01/14/2015

**PeRC PREA Subcommittee Meeting Minutes
December 3, 2014**

PeRC Members Attending:

Wiley Chambers

George Greeley

Kevin Krudys

Dionna Green

Dianne Murphy

Kristiana Brugger

Colleen LoCicero

Julia Pinto

Greg Reaman ((b) (4) review only)

Hari Cheryl Sachs

Michelle Roth-Cline

Karen Davis-Bruno

Peter Starke

Olivia Ziolkowski

Rosemary Addy

Barbara Buch

Nisha Jain ((b) (4) review only)

Adrienne Hornatko-Munoz ((b) (4) only)

PREA



(b) (4)

	NDA	206073	Glyxambi (empagliflozin/linagliptin) Full Waiver	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate
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(b) (4)



(b) (4)

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Glyxambi Full Waiver

- Proposed Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate
- This application triggered PREA as a new: active ingredient, indication, dosage form, dosing regimen, route of administration.
- The PDUFA goal date is January 30, 2015
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impractical because there are too few patients in the pediatric population appropriate for such a study (estimated to be 1% of the pediatric T2DM population).



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/s/

GEORGE E GREELEY
12/22/2014

From: CappelLynch, Callie
To: chung.lee-sogaard@boehringer-ingelheim.com
Bcc: [Guettier, Jean-Marc](#)
Subject: NDA 206073 Labeling Comments
Date: Monday, December 08, 2014 12:40:00 PM
Attachments: [Empagliflozin_Linagliptin_US_PI_FDA comments 12.8.14.docx](#)

Hi Chung,

Please see the attached PI for NDA 206073 with FDA comments. If you have any questions, please let me know. Please respond to these comments by COB December 17, 2014.

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 you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "COMPANY'S response to FDA change or COMPANY comment."

Thanks,

Callie Cappel-Lynch
Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-8436

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/s/

CALLIE C CAPPEL-LYNCH
12/08/2014

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the 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. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: 206073

PRODUCT PROPRIETARY NAME: Glyxambi

ESTABLISHED/GENERIC NAME: empagliflozin and linagliptin

APPLICANT/SPONSOR: Boehringer Ingelheim

PREVIOUSLY APPROVED INDICATION/S:

- (1) none
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) *adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate* _____
- (2) _____
- (3) _____
- (4) _____

BLA/NDA STAMP DATE: 1/30/2014

PDUFA GOAL DATE: 1/30/2015

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

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

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

Did the sponsor submit an Agreed iPSP? Yes ***No***

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ***No***

- ***In response to the initial PSP, a non-agreement letter was issues requesting the PSP be amended to request a full waiver (see Non-agreement letter and memorandum to file submitted to IND-108388 on Februrary 7, 2014).***

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ***No***

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ***No***

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ***No***

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived. All pediatric age groups
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. *Provide justification for Waiver:*

Appropriate studies to support the safety and effectiveness of this fixed dose combination product would require enrollment of patients for whom use of three or more antidiabetic agents are needed. The population of patients appropriate for such a study are small (estimated to be 1% of the pediatric T2DM population) and are impractical. Additionally, the fixed dose combination product does not provide any meaningful therapeutic benefit over the use of the separate individual products.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

No proposed changes.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

basal cell and squamous cell skin cancer

bladder

breast

cervical

colorectal

endometrial

esophageal

cancer (continued):

follicular lymphoma

gastric

hairy cell leukemia

hepatocellular

indolent non-Hodgkin lymphoma

lung (small & non-small cell)

multiple myeloma

oropharynx (squamous cell)

ovarian (non-germ cell)

pancreatic

prostate

refractory advanced melanoma

renal cell

uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

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/s/

CALLIE C CAPPEL-LYNCH
11/19/2014

From: CappelLynch, Callie
To: "chung.lee-sogaard@boehringer-ingelheim.com"
Subject: RE: NDA 206073: empagliflozin + linagliptin FDC
Date: Friday, October 10, 2014 11:40:00 AM
Attachments: [image001.png](#)
[PI FDA comments 10.10.14 comments.docx](#)

Hi Chung,

Please see the labeling comments attached for NDA 206073. We do not anticipate any new PMR/PMCs at this time, however our reviews are not finalized. We will update you on this closer to the goal date.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingelheim.com [mailto:chung.lee-sogaard@boehringer-ingelheim.com]
Sent: Wednesday, October 08, 2014 11:21 AM
To: CappelLynch, Callie
Subject: RE: NDA 206074: empagliflozin + linagliptin FDC

Thank you Callie.
Chung.

Chung Lee-Søgaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingelheim.com

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Wednesday, October 08, 2014 11:20 AM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Subject: RE: NDA 206074: empagliflozin + linagliptin FDC

Hi Chung,

We still expect to send comments by the previously communicated date. If this changes, I will let you know.

Thanks,
Callie

From: chung.lee-sogaard@boehringer-ingelheim.com [mailto:chung.lee-sogaard@boehringer-ingelheim.com]
Sent: Wednesday, October 08, 2014 11:13 AM
To: CappelLynch, Callie

Subject: NDA 206074: empagliflozin + linagliptin FDC

Dear Callie,

I was wondering if you might have any information regarding potential labeling comments on October 13th (as per filing letter) and the late-cycle meeting on October 30th. It would be very helpful from a planning perspective.

Thank you in advance.
Chung.



Chung Lee-Søgaard, Ph.D.

Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT

P: 203 798 4224 :: C: (b) (6)

chung.lee-sogaard@boehringer-ingelheim.com



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/s/

CALLIE C CAPPEL-LYNCH
10/10/2014

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 10, 2014

Application Number: NDA 206073

Product Name: empagliflozin/linagliptin tablets

Sponsor/Applicant Name: Boehringer Ingelheim

Subject: Clarification on Site Close Out Letter sent to FDA

FDA Participants

Cynthia Kleppinger, M.D.

Medical Officer, Office of Scientific Investigations (OSI)

Callie Cappel-Lynch, Pharm.D.

Regulatory Project Manager, Division of Metabolism and Endocrinology Products (DMEP)

Sponsor Participants

Debbie Clark

Compliance

Ashish Singh

Clinical Trial Management

Renee Kaste

Trial Clinical Monitor

Sujata Bhowal

Local Monitor

1.0 BACKGROUND:

On April 9, 2012, in accordance with 21 CFR 312.31, Boehringer Ingelheim (BI) informed FDA of a site closure for Dr. Farid Marquez, site 1063, in study 1275.1 being conducted under IND 102, 145 (Sequence Number 0101). Reference was also made to IND 108388 study 1245.25 (Sequence Number 0071). The investigator information for Dr. Farid Marquez (Form 1572 and CV) was submitted to IND 108388 on September 2, 2011 (SN 0011/SEQ 0009). On April 24, 2012, BI received a response and request for additional information from Dr. Marquez, with a denial of any fraudulent activity at his site. BI provided a response to Dr. Marquez in a letter dated May 7, 2012, which included an outline of the details of their findings. These documents were also forwarded to the FDA.

Subsequently, in the original NDA 206073 submitted to FDA on January 30, 2014, the clinical study report for 1275.1, Section 9.6, identified one site (1063, later confirmed by sponsor to be Dr. Farid Marquez) where fraudulent activity was suspected and then confirmed by an independent auditor. Data from this site is not being used to support the application. On Friday September 5, 2014, FDA sent an information request to BI requesting copies of all monitoring reports for this site. On September 8, 2014, BI responded to this request. On September 9, 2014, FDA requested that the sponsor provide the subject numbers with questionable records and quality management investigation reports. On September 9, 2014, BI also responded to this request. At this time the company also agreed to a teleconference with FDA so that remaining issues could be clarified.

2.0 DISCUSSION:

BI confirmed that they have not been involved with any other protocols with Dr. Farid Marquez other than those previously mentioned (1275.1 and 1245.25). BI confirmed that Dr. Farid Marquez had denied any previous FDA inspection and subsequent Form FDA-483 when questioned at site qualification visits. BI walked through the history of events leading up to the closure of the site. BI confirmed that an independent auditor contacted the private physicians by phone and faxed to them redacted documents for their review and signature confirmation. There were eight documents in question. The auditor was able to contact six of the eight private physicians. Five of the six sent back written confirmation that the document was not theirs and the signature was not theirs. The sixth physician verbally confirmed the same. BI staff is not aware of exactly who at the site developed the fraudulent documents. BI confirmed that a letter was sent to Dr. Farid Marquez at site closure stating that several medical records contained signatures of physicians that did not sign the documents. The IRB was informed in a letter dated April 5, 2012 of the site closure but the IRB was not requested to also contact the private physicians.

3.0 ACTION ITEMS:

BI will provide written follow-up. FDA asked that BI submit a copy of the sponsor questionnaire that included the question regarding the previous Form FDA-483 received by the site.

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/s/

CALLIE C CAPPEL-LYNCH
09/11/2014

From: CappelLynch, Callie
To: chung.lee-sogaard@boehringer-ingelheim.com
Subject: NDA 206073 Labeling Request
Date: Wednesday, August 27, 2014 1:59:00 PM

Hi Chung,

We are continuing review of NDA 206073 and request that you submit updating labeling using language based on the recently approved empagliflozin label. If you have any questions, please contact me.

Thanks,

Callie Cappel-Lynch
Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-8436

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/s/

CALLIE C CAPPEL-LYNCH
08/27/2014



NDA 206073

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs, BIPI
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Sogaard:

Please refer to your New Drug Application (NDA) dated January 29, 2014, received January 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for empagliflozin and linagliptin tablets; 10 mg/5 mg and 25 mg/5 mg .

We also refer to the teleconference between representatives of your firm and the FDA on July 9, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 9, 2014 12:00pm-1:00pm

Application Number: 206073

Product Name: empagliflozin and linagliptin tablets

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: William Chong

Meeting Recorder: Callie Cappel-Lynch

FDA ATTENDEES

William Chong, M.D.	Clinical Team Leader, Acting, Division of Metabolism and Endocrinology Products (DMEP)
Jennifer Pippins, M.D.	Deputy Director for Safety, Acting, DMEP
Julie Van der Waag, M.P.H.	Chief Project Management Staff, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Lokesh Jain, Ph.D.	Team Leader, Office of Clinical Pharmacology (OCP)
Sury Sista, Ph.D.	Reviewer, OCP
Mark Rothmann, Ph.D.	Team Leader, Office of Biostatistics (OB)
Jennifer Clark, Ph.D.	Reviewer, OB
Neil Vora, Pharm.D.	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Kareen Riviere, Ph.D.	Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)
Shawna Hutchins, Pharm.D.	Patient Labeling Reviewer, Office of Medical Policy (OMP)
David Carlson, Ph.D.	Non-clinical Reviewer, DMEP
Erika Pfeiler, Ph.D.	Microbiology Review, ONDQA

APPLICANT ATTENDEES

Uli Broedl, M.D.	Associate Therapeutic Area Head
Anette Brunner-Schwarz, Ph.D.	R&D project management
Dan Coccozza	Data management
Kathryn Jason, PhD.	Regulatory
Arno Kalkuhl, Ph.D.	Research and development
Renee Kaste, Ph.D.	Clinical operations

Gabriel Kim, M.D.	Pharmacovigilance
Sven Kohler, M.D.	Pharmacovigilance
Chung Lee-Sogaard, Ph.D.	Regulatory
Dacheng Liu, Ph.D.	Statistics
Joanne Palmisano, M.D.	Vice president, Regulatory
Sanjay Patel, M.D.	Clinical
Joerg Pfeifer, Ph.D.	Regulatory, Lilly
Heidi Reidies	Regulatory
Jim Segretario, Ph.D.	CMC RA
Michael Shear	Statistics
Jan-Markus Wolters, Ph.D.	Project management

1.0 INTRODUCTION

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

2.0 SIGNIFICANT ISSUES

Clinical

1. Only one significant issue has been identified to date. There is an apparent lack of additional efficacy of the empagliflozin and linagliptin 25 mg/5 mg combination over empagliflozin 25 mg alone in the treatment naïve study population.

3.0 INFORMATION REQUESTS

There are no information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The late cycle meeting is scheduled for October 30, 2014, 12:00pm-1:00pm.

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/s/

JENNIFER R PIPPINS

07/10/2014

For Dr. Guettier

From: CappelLynch, Callie
To: ["chung.lee-sogaard@boehringer-ingelheim.com"](mailto:chung.lee-sogaard@boehringer-ingelheim.com)
Subject: RE: NDA 206073 --- lina/empa
Date: Tuesday, June 10, 2014 9:38:00 AM

Hi Chung,

We are working on review of the responses you provided in response to our filing communication letter. We note that in response to questions 3 and 4 you informed us that you are still evaluating the options we presented. We remind you that this information is required to complete our review and request that you provide an adequate response by July 1, 2014. If you have any questions, please contact me.

Best Regards,
Callie

From: chung.lee-sogaard@boehringer-ingelheim.com [mailto:chung.lee-sogaard@boehringer-ingelheim.com]
Sent: Monday, June 09, 2014 4:22 PM
To: CappelLynch, Callie
Subject: RE: NDA 206073 --- lina/empa

Dear Callie,

I wanted to let you know that we submitted the responses to the remaining potential review issue items identified in the filing communication letter yesterday, June 10th (SEQ 008).

Thank you.
Chung.

Chung Lee-Sogaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingelheim.com

From: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Sent: Tuesday, June 03, 2014 8:08 AM
To: CappelLynch, Callie
Subject: RE: NDA 206073 --- lina/empa

Dear Callie,

I wanted to let you know that we submitted the requested information for request #2 in the filing communication (June 2/SEQ 0006). The responses for the remaining requests will be submitted shortly in a separate submission.

Thank you.
Chung.

Chung Lee-Søgaard, Ph.D.
Drug Regulatory Affairs
Boehringer-Ingelheim Pharmaceuticals, Inc.
Tel: 1-203-798-4224
Fax: 1-203-791-6262
Email: chung.lee-sogaard@boehringer-ingelheim.com

From: Chiang, Raymond [<mailto:Raymond.Chiang@fda.hhs.gov>]
Sent: Friday, April 11, 2014 1:33 PM
To: Lee-Sogaard,Dr.,Chung (DRA) BIP-US-R
Cc: CappelLynch, Callie
Subject: RE: NDA 206073 --- lina/empa

Hi Chung,
See attached filing issues identified letter for NDA 206073. This letter was signed by me on behalf of Dr. Jean-Marc Guettier.
As always, please confirm receipt of email.
Thanks,
Ray

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/s/

CALLIE C CAPPEL-LYNCH
06/10/2014

From: CappelLynch, Callie
To: chung.lee-sogaard@boehringer-ingenheim.com
Subject: NDA 206073 Information Request
Date: Wednesday, June 04, 2014 9:47:00 AM

Hi Chung,

Please see the information request below for NDA 206073:

1. Provide your plan for Validation of the Empagliflozin/Linagliptin tablet manufacturing process.
2. Identify the Reference Standards for the drug substances empagliflozin and linagliptin used for the identification and quantitation of both drug substances and the quantitation of their degradation products in empagliflozin/linagliptin tablets.
3. Provide the water vapor permeation rate of the aluminum (b) (4) blisters used as a container closure for empagliflozin/linagliptin tablets 10 mg/5 mg and 25 mg/5 mg.

We are requesting your response by June 25, 2014 . If you have any questions, or need clarification, please contact me.

Thanks,

Callie Cappel-Lynch
Regulatory Project Manager
Food and Drug Administration
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-8436

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/s/

CALLIE C CAPPEL-LYNCH
06/04/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206073

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

ATTENTION: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Lee-Sogaard:

Please refer to your New Drug Application (NDA) dated January 29, 2014, received January 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin and Linagliptin Tablets, 10 mg/5 mg and 25 mg/5 mg.

We also refer to your correspondence, dated and received March 13, 2014, requesting review of your proposed proprietary name, Glyxambi.

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

If any of the proposed product characteristics as stated in your March 13, 2014, 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 Lyle Canida, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1637. For any other information regarding this application, contact Callie Cappel-Lynch, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
05/09/2014



NDA 206073

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs, BIPI
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Sogaard:

Please refer to your New Drug Application (NDA) dated January 29, 2014, received January 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for empagliflozin/linagliptin tablets; 25 mg/5 mg and 10 mg/5 mg.

We also refer to your amendments dated February 24, March 6, and 13, 2014.

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**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is January 30, 2015.

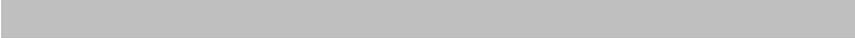
We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes 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 October 13, 2014. In addition, the planned date for our internal mid-cycle review meeting is June 24, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

Biopharmaceutics

1. Provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
2. Submit SAS Transport files of the pharmacokinetic data from the BE study. The data should include Time, Concentration, AUC0-t, AUC0-inf, Cmax, Tmax, Kel, and T1/2. Please submit two sets of data in the following format:
 - SUBJ SEQ PER TRT Time Concentration;
 - SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf.

Quality Micro

3. You propose to perform skip lot testing for the Microbial Limits test for drug product release. Skip-lot testing for drug products is not allowed by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points:
 - Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
 -  (b) (4)
 - 
 - Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
 - Describe activities taken when microbiological acceptance criteria are not met at control points.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. Please submit a

revised drug product release specification for whichever microbial limits testing alternative that you select.

4. Your release and stability specifications include microbial limits and the absence of *Escherichia coli*, but you do not describe testing methods. Describe these methods and state whether validation has been performed to ensure that these methods are adequate for use with the drug product.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Metabolism and Endocrinology (DMEP). Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RAYMOND S CHIANG
04/11/2014

From: Chiang, Raymond
To: chung.lee-sogaard@boehringer-ingelheim.com
Subject: NDA 206073 --- lina/empa
Date: Tuesday, April 08, 2014 10:23:00 PM

Hi Chung,
See request from the DMEPA/OSE reviewer. I will let you know the mid-cycle meeting date soon.
Thanks,
Ray

I am conducting the Labels and Labeling review for Glyxambi and I noticed that the Applicant mentioned in their Request for Proprietary Name Review cover letter (dated March 13, 2014) that "the colors used in draft labels are not final and may be revised".

Would you mind sending a request to the Applicant for a submission of their labels (with their color schemes finalized) by the mid-cycle meeting? This will ensure that DMEPA has enough time to review the submission, if the Applicant chooses to revise the colors.

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

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

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/s/

RAYMOND S CHIANG
04/08/2014

From: Chiang, Raymond
To: ["chung.lee-sogaard@boehringer-ingenheim.com"](mailto:chung.lee-sogaard@boehringer-ingenheim.com)
Subject: RE: Lina/empa FDC --- NDA 206073
Date: Monday, March 31, 2014 2:55:00 PM

Hi Chung,

See below (in black font) information request from the FDA medical officer and from our clinical site inspection (OSI) staff.

As always, please confirm receipt of email.

Thanks,
Ray

From OSI:

In your clinical study report for 1275.1, Section 9.6, you identify one site (1063) where fraudulent activity was suspected and then confirmed by an independent auditor. Please supply the name, contact information and CV of this site. It cannot be found in the document "16.1.4 List and description of investigators and sites".

In your February 24, 2014 response to the information request sent by email from Mr. Raymond Chiang, Regulatory Project Manager on February 11, 2014, you state that the discrepancy noted in the clinsite.xpt file and the CSR is due to the fact that three sites (1063, 1021, and 1111) had fraudulent activities for which data was excluded from analyses. (Site 1021 is Dr. Robert Eyzaguirre with three enrolled subjects and Site 1111 Dr. David Wyatt with one enrolled subject). Please explain why these two additional sites were not included in the clinical study report discussion.

We need complete information regarding the fraudulent activities found. Please supply the amendment number and dates when the information about these three sites was sent to IND 108388.

From DMEP medical officer:

-

The DM.xpt file contains 1405 subjects while the clinical study report states that 1363 subjects were used for analysis (both for safety and for efficacy). We are unable to ascertain the reason for this discrepancy from review of the study report. Even considering those subjects which you report as excluded from analysis due to duplicate enrollment and/or scientific misconduct (from section 10, there were 49 subjects excluded from the metformin background population and 12 subjects excluded from the treatment naïve population), we are unable to reconcile the numbers. Provide us with the following additional information:

1. Explain the difference between the number of subjects listed in the submitted datasets and the number of subjects analyzed in the study report.

2. Provide a listing of those subjects in the dataset not included in the analyses along with a reason for not including each subject.

In addition, the following information is requested to clarify questions raised by our ongoing review of the data.

1. The following study subject ID's are associated with a serious adverse event as reported in the AE.xpt file:

1275-0001-93325	1275-0001-99701
1275-0001-93525	1275-0001-90846
1275-0001-91361	1275-0001-92042
1275-0001-93617	1275-0001-94967
1275-0001-92094	1275-0001-92300
1275-0001-94387	1275-0001-93693
1275-0001-98041	1275-0001-965772

Provide your rationale for not including these patients in your analysis of serious adverse events.

2. Study subject 1275-0001-094967 is encoded as having a serious adverse event in the submitted AE.xpt dataset. No narrative can be located for this patient. Provide us with a narrative of the serious adverse event and the rationale for not including this patient in your analysis.

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/s/

RAYMOND S CHIANG
03/31/2014



NDA 206073

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs, BIPI
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Sogaard:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Empagliflozin/Linagliptin Tablets; 25 mg/5 mg and 10 mg/5 mg

Date of Application: January 29, 2014

Date of Receipt: January 30, 2014

Our Reference Number: NDA 206073

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 March 31, 2014, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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 conform to the content and format requirements of revised 21 CFR 201.56-57.

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang MPT, MS, MS
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/

RAYMOND S CHIANG
03/27/2014

From: Chiang, Raymond
To: ["chung.lee-sogaard@boehringer-ingenheim.com"](mailto:chung.lee-sogaard@boehringer-ingenheim.com)
Subject: RE: Informatoin request from OSI/FDA --- NDA 206073
Date: Tuesday, February 11, 2014 3:07:00 PM

Hi Chung,

See below information request from our OSI colleagues. They are requesting a response ASAP. Please confirm that you have received this email.

Thanks,

Ray

1. We need help finding our Part 1 and Part 2 information. The Reviewer's Guide says that site level information (was to be linked but is not) for the pivotal Study 1275.1 is provided in Module 5.3.5.4. We cannot find it

I - Clinical Investigator Information nor II – Subject Level Data Listings by Site. If the sponsor could tell us where it is.

2. For Study 1275-0001 we are unable to reconcile the number of sites that entered subjects and the numbers of entered subjects between data provided in the clinsite.xpt file for use in CDER's Clinical Site Selection Tool and the data described in the Clinical Study Report (CSR); please explain these discrepancies. For example:

1. The clinsite.xpt file contains data for 191 clinical sites that entered (i.e. randomized and treated) at least one subject, but the CSR describes 194 sites as having entered at least one subject.
2. The clinsite.xpt file appears to contain data for 1363 entered subjects (686 in pre-treatment arms and 677 in treatment naïve arms), but the CSR describes 1374 entered subjects (691 in pre-treatment arms and 683 in treatment naïve arms).

The discrepancies do not appear to be explained by exclusion of subjects from Site #1063 for GCP non-compliance (26 entered subjects) or from exclusion of subjects screened/enrolled at more than one site (23 subjects).

In addition, please confirm that screen and enroll numbers reported in clinsite.xpt are correctly reported (or provide corrected values). For example:

	Site Number	Enroll/screen (from clinsite.xpt)
1275-0001 "Naïve"		
	1025	5/3
	1110	6/4
	1080*	6/5
	96002	11/10
1275-0001 "Pre-TRT"		
	1007	11/10
	1110	12/9

| 96006

| 3/4

*For Site #1080 clinsite.xpt displays 6 entered subjects, which is discrepant with DM.xpt display of 5 entered subjects

3. We would also like a complete list of investigators (i.e. the CSR only has the top enrolling CI for each country).

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/s/

RAYMOND S CHIANG
02/11/2014



IND 108388

MEETING REQUEST CANCELLED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Lee-Sogaard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for empagliflozin/linagliptin fixed-dose-combination (FDC) tablets.

We also refer to your July 30, 2013, email communication requesting cancellation of the meeting we scheduled on July 31, 2013, in response to your May 31, 2013, meeting request because you consider your proposals for the NDA in the meeting package and your responses to FDA's preliminary comments to represent the content of a complete application. The July 31, 2013, meeting has been cancelled.

Because the application that was the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, the pre-submission meeting was intended to include discussion and agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. At the meeting, you and FDA might have also reached agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Although the meeting has been cancelled, the following agreements have been made. They are summarized below:

1. Regarding the content of a complete application: We repeat our preliminary comments, your response, if any, and the agreement reached prior to the pre-NDA meeting that resulted in your suggestion to cancel the meeting.

2. Note that all applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
3. A preliminary discussion on the need for a REMS: **Please refer to the discussion and comments related to question #9.**
4. We note that you have not proposed late submission of minor application components. **Therefore, your application is expected to be complete at the time of original submission.**
5. We remind you of the “Additional Important Information” and information requests from the Office of Scientific Investigation (OSI) that were included in the preliminary comments.

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1

In Module 3 of the empagliflozin + linagliptin FDC tablets NDA, BI plans to include complete drug product and regional sections (3.2.P and 3.2.R) for empagliflozin + linagliptin FDC tablets. Throughout Module 3, sections where no information is filed will be omitted from the NDA submission per ICH Guidance for Industry M4: The CTD – General Questions and Answers, December 2004. These sections will be identified in both the NDA cover letter and the reviewer's guide. Tentatively, the sections BI will not include are: 3.2.P.3.5 Process Validation and/or Evaluation, and 3.2.P.4.6 Novel Excipients. Section 3.2.P.6 Reference Standards or Materials will also not be included; however, BI will refer to the relevant information in the linagliptin and empagliflozin NDAs, 201280 and 204629, respectively. Additional sections for which no information is filed may be added to this list. The drug substances used for the empagliflozin + linagliptin FDC tablets (b) (4) described in NDA 204629 for empagliflozin which will be under review, and to the approved NDA 201280 for linagliptin. Therefore, BI plans to refer to the drug substance information in the empagliflozin and linagliptin NDAs and does not plan to include any drug substance documentation in Module 3.2.S of the empagliflozin + linagliptin FDC NDA.

In addition, it is proposed to provide in Module 2 of the empagliflozin + linagliptin FDC NDA a Quality Overall Summary (QOS) which will summarize the new drug product information. A table of contents for Module 3 is provided in Section 10.2.

Does the Division have any comments about the proposed approach for Module 3 and QOS of the empagliflozin + linagliptin FDC NDA?

FDA Pre-Meeting Response

We agree with your proposed Module 3 sections and QOS of the new NDA. We remind you to include in the NDA a complete list of all testing and manufacturing facilities used for the drug substances and drug product in Form 356h of the NDA, with detailed contact information and a statement that all facilities are ready for the GMP inspection at the time of the NDA submission.

FDA Comment

Boehringer Ingelheim Pharmaceuticals, Inc (BI) agrees with FDA comments. BI and FDA have reached agreement on this item.

Nonclinical

Question 2

In Module 4 of the empagliflozin + linagliptin FDC NDA, BI plans to include only those nonclinical reports specifically assessing the nonclinical safety of concomitant administration of empagliflozin and linagliptin. A table of contents for Module 4 is provided in Section 10.2. In addition, BI plans to cross-reference reports and datasets previously provided in Module 4 of the empagliflozin NDA and the linagliptin NDA. BI proposes that the new reports for concomitant administration, and nonclinical information cross referenced to the NDAs, will fulfill the requirement of the Nonclinical Summary (Module 2.6); therefore, no additional summary documents are planned to be provided.

- a) Does the Division have any comments regarding the general organization and/or proposed content to be included in Module 4 of the NDA?

FDA Pre-Meeting Response

We prefer that you also include non-clinical written and tabulated summaries that address the additional studies conducted to support the FDC. It is acceptable to cross-reference the monotherapy NDAs for the other toxicology studies.

- b) Does the Division have any comments on the proposed plan?

FDA Pre-Meeting Response

The content of Module 4 appears appropriate, but please see the response to question 2a above.

FDA Comment

BI agrees with the FDA proposal in response to question 2a. BI and FDA have reached agreement on items 2a and 2b.

CLINICAL

The clinical information for the empagliflozin + linagliptin FDC NDA will comprise the final reports of one pivotal Phase III clinical study (1275.1) and two Phase I clinical pharmacology studies in healthy volunteers (1245.30 [drug to drug interaction study] and 1275.3 [relative bioavailability study]). The two Phase I study reports have been previously submitted to NDA 204629 for empagliflozin tablets and to IND 108388 for the empagliflozin + linagliptin FDC. These three reports will make up the totality of clinical information from completed studies using the combination of empagliflozin + linagliptin.

- Study 1275.1: A phase III, randomized, double-blind, parallel group study to evaluate the efficacy of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control (metformin treated: N=665 [planned], N= 684 [actual]; treatment-naïve: N=665 [planned], N= 677[actual])
- Study 1245.30: Relative bioavailability of multiple doses BI 10773 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of BI 10773 50 mg and linagliptin 5 mg administered alone to healthy male volunteers (an open-label, randomised, crossover, clinical phase I study) (N=16)
- Study 1275.3: Relative bioavailability investigations of a 25 mg BI 10773/5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single dose, crossover, Phase I trial in healthy male and female volunteers) (N=42)

Two additional studies will be ongoing at the time of the NDA submission (Studies 1275.9 and 1275.10). The only data included for these studies will be narratives and CRFs for patients with serious adverse events that qualify for expedited reporting (SUSARs).

- Study 1275.9: A phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.
- Study 1275.10: A phase III, randomized, double-blind, parallel group study to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combination with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks of treatment with empagliflozin 10 mg or 25 mg on metformin background therapy.

A table of contents for Module 5 is provided in Section 10.2.

Question 3

- a) Does the Division have any comments regarding the general organization and/or proposed content to be included in Module 5 of the NDA?

FDA Pre-Meeting Response

Clinical:

The proposed organization for module 5 appears acceptable.

Question 3b) Does the Division have any comments on the proposed plan?

FDA Pre-Meeting Response and Question:

Clinical:

Please provide your rationale for not submitting the final study reports for studies 1275.9 and 1275.10 at the time of submission of your NDA. Additionally, clarify if there are any other studies not listed in the pre-NDA meeting package where subjects are exposed to the combination of empagliflozin and linagliptin.

Please clarify what is meant when you use the acronym SUSAR. In the “Question” section of the meeting package you state that SUSARs are serious adverse events that qualify for expedited reporting and then in section 10.6 define it as a serious unexpected suspected adverse reaction. In addition, narratives and CRFs as listed for the completed trials in section 10.4 should be submitted for the ongoing studies.

BI pre-meeting response to FDA query:

Studies 1275.9 and 1275.10 began enrolling patients in the first quarter of 2013, and will be ongoing and blinded at the time of the submission; the final clinical study reports are planned to be available in early 2015.

The design of each of these trials includes a 16 week treatment period with either linagliptin or empagliflozin monotherapy prior to randomized treatment with the combination product. The number of patients exposed to the combination of empagliflozin and linagliptin at the time of data cutoff for this NDA is expected to be approximately 45 patients in 1275.9 and 50 patients in 1275.10.

There are no other studies where subjects are exposed to the combination of empagliflozin and linagliptin (see also response to FDA comment to Question 8). The studies listed above make up the totality of the clinical studies with any subjects exposed to the combination of empagliflozin and linagliptin.

SUSARs are defined as suspected unexpected serious adverse reactions. Reports of suspected unexpected serious adverse reactions are unblinded by BI during the conduct of the trial for appropriate review and handling.

*For ongoing blinded studies (1275.9 and 1275.10), BI expects that most of the cases requested will also be considered as suspected unexpected serious adverse reactions, and **thus will be unblinded**; narratives and CRFs will be provided for these. Additionally, BI will provide a blinded listing of the requested adverse events for which narratives and CRFs are not provided. If further information is needed, BI can provide that upon request.*

Is this proposal acceptable?

FDA Request / Comment

FDA asked for confirmation that the final study report to be submitted for Study 1275.1 will encompass the 52 week data. BI confirmed, via email, that 52-week data would be submitted.

FDA concurred with BI's response. Agreement was reached on these items.

Question 4

The single entity tablets empagliflozin and linagliptin that were used in the pivotal safety and efficacy Study 1275.1 and the relative bioavailability Study 1275.3 are equivalent formulations to the to-be-marketed empagliflozin 10 and 25 mg tablets described in NDA 204629 (submitted March 5, 2013) and to the marketed TRADJENTA 5 mg tablets described in NDA 201280 (approved May 2, 2011). At the start of study 1275.1, the empagliflozin + linagliptin FDC tablets in Study 1275.1 were (b) (4) empagliflozin + linagliptin FDC tablets used in the bioavailability Study 1275.3, which supports equivalence of the FDC to its components. During the 1275.1 trial, there was a minor change to the quantitative composition of the FDC tablets.

(b) (4)
in the FDC tablets when compared to the FDC tablets used in 1275.3 and first used in trial 1275.1. This change was not deemed to impact the bioavailability of the active components. Considering these data, BI believes that reference to the NDAs for the individual drug products to support safety and efficacy of empagliflozin and linagliptin is appropriate. Does the Division concur with BI's approach?

FDA Pre-Meeting Response

Biopharmaceutics:

This submission did not include a comparative qualitative and quantitative composition of the FDC formulation for the pre- and post change. However, based on the percent change mentioned in the question above, this manufacturing change could be considered minor requiring dissolution profiles comparisons. Therefore, to support the bridging of these formulations, provide the following information in the NDA submission:

1. Comparative qualitative and quantitative composition of the FDC formulation for both strengths of your product for the pre- and post change.
2. Comparative dissolution data using the regulatory dissolution method for each FDC tablet strength manufactured pre- and post- the proposed changes. Also, provide individual (n=12), mean, minimum, maximum, RSD, profile data, and calculate the similarity factor f2 values.

Additional Biopharmaceutics Comments

General comments to consider for information expected at the time you plan to submit your proposed dissolution method:

1. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e.*, selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label

amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

2. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
3. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.
4. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e. specification-sampling time point and specification value) for both components of the proposed product.
5. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

6. Per CFR §320.22 and the Guidance for Industry “Bioavailability and Bioequivalence Studies for Orally Administered Drug Product – General Considerations”, the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the bioequivalence of the lower strength (10 mg empaglifolzin/5 mg linagliptin) can be waived if you submit a biowaiver request and meet the following criteria:
 - The lower strength is (b) (4) in its active and inactive ingredients to the higher strength.
 - Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.
 - There is BA/BE data for the highest strength.

BI Pre-Meeting Response and Question:

Regarding the specification for dissolution (Biopharmaceutics Additional Comments 4 and 5), BI will include a disintegration test in the specification for the drug product in lieu of dissolution. Data will be presented in the NDA supporting this choice based on decision tree #7 of ICH Q6A.

Is this proposal acceptable?

FDA Additional Pre-Meeting Comments regarding BI's Response and Question

Yes, your proposal is acceptable. The following supportive information/data described in the ICH Topic Q6A document should be provided in the NDA to support your proposal of using the disintegration test in lieu of the dissolution test:

- a. Solubility profiles for the drug substance throughout the physiological pH range (1.2 to 6.8).**
- b. Dissolution profiles of the proposed drug product at pH 1.2, 4.0 and 6.8.**
- c. Data showing a relationship between dissolution and disintegration or data showing that disintegration is more discriminating than dissolution.**
- d. The complete development and validation data for the dissolution method.**
- e. Information on the formulation and process factors that may impact dissolution/disintegration (i.e., amount of disintegrant, surfactant, and lubricant).**

Since our recommendation regarding the acceptability of using disintegration instead of dissolution is a review issue under the NDA, you should include complete dissolution as well as disintegration data in your NDA submission. Additionally, note that a dissolution method should be available for your product to support future SUPAC changes under post-approval supplements.

FDA concurred with BI's response. BI agreed to provide the additional information described above at the time of NDA submission. Agreement was reached on this issue.

Question 5

The pivotal Phase III trial 1275.1 is a 52 week study to evaluate the efficacy and safety of empagliflozin + linagliptin FDC tablets compared to the individual components with primary efficacy analysis at 24 weeks. The final clinical trial report of the 52 week study, which will include the data from the primary analysis at 24 weeks, will be submitted in the NDA. The clinical trial report for the analysis of the data at 24 weeks is currently in preparation; BI is including a summary of the key safety and efficacy results in Section 10.3 and the draft clinical trial report in Module 1.11.3. The study is continuing with blinding in place for all personnel who continue to be involved in the operation and evaluation of the study to week 52.

- a) Do the results for the 24 week primary analysis of 1275.1 support the safety and efficacy for the FDC as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and empagliflozin is appropriate?

FDA Pre-Meeting Response:

Clinical:

We concur that the primary endpoint may be measured at 24 weeks. We prefer that the 52 week information (particularly safety information) also be submitted at the time of the initial fixed dose combination NDA submission. This is because, in distinction to the majority of approved fixed dose combinations for type 2 diabetes, this FDC consists of two very new products: empagliflozin, which is not yet approved at all; and linagliptin, which was only recently approved. Most approved fixed dose combinations include at least one component for which we have a long safety experience, for example combinations with metformin or sulfonylurea.

Statistical:

Your primary analysis uses the LOCF method for dealing with missing data which is no longer recommended by the Division since the publication of a report on missing data by the National Academy of Sciences (NAS, 2010), *The Prevention and Treatment of Missing Data in Clinical Trials*. The report states “The panel believes that in nearly all cases, there are better alternatives to [LOCF]... which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects”. We suggest that you submit an amendment for your Statistical Analysis Plan (SAP) to propose a statistical analysis which does not rely on LOCF and which is in line with NAS recommendations before submitting the NDA.

BI response:

Statistical: Study 1275.1 has already been unblinded and analyzed for the primary endpoint at 24 weeks. The SAP can no longer be changed. However, to address FDA’s request, BI will provide an amendment to the SAP using an alternative method to LOCF.

Is this proposal acceptable?

FDA concurred with BI’s response. Agreement was reached on these issues.

Question 6

- a) Section 10.4 outlines which case report forms (CRFs) BI proposes to include in the empagliflozin + linagliptin NDA. Does the Division concur with BI’s proposal?

FDA Pre-Meeting Comments:

Clinical:

We agree with the proposed list of CRFs to be submitted for the completed trials. CRFs from the ongoing blinded studies should be submitted based on the same list.

BI response:

For ongoing blinded studies (1275.9 and 1275.10), BI expects that most of the cases requested will be unblinded, and narratives and CRFs will be provided. As indicated in our response to FDA comments on Question 3b, additionally, BI will provide a blinded listing of the requested adverse events for which narratives and CRFs are not provided.

Is this proposal acceptable?

- b) Section 10.4 outlines which case narratives BI proposes to include in the empagliflozin + linagliptin NDA. Does the Division concur with BI's proposal?

FDA Pre-Meeting Comments:

Clinical:

We agree with the proposed list of CRFs to be submitted for the completed trials. CRFs from the ongoing blinded studies should be submitted based on the same list. For the proposed hyper-linked table in section 15.4.3 of the clinical study report and in module 5.3.5.1 listing all the subjects with narratives and case report forms, also include the associated MedDRA preferred term(s) and treatment assignment.

BI response:

Please see BI's response to Question 3b and above to Question 6a.

FDA concurred with BI's response. Agreement was reached on this issue.

Question 7

BI will provide full datasets for the pivotal phase III study 1275.1. BI will provide the datasets developed for the 52-week efficacy and safety analysis only. A sensitivity assessment on the primary efficacy endpoint at 24 weeks will be incorporated additionally into the 52-week clinical trial report in order to demonstrate that potential database updates which followed completion of the 24-week primary analysis had no influence on the results obtained. The tabular datasets will be provided in SDTM and the analysis datasets in ADaM format.

BI will provide limited tabular datasets (SDTM) for the phase I studies in healthy volunteers (Studies 1245.30 and 1275.3).

A full description of the proposal for datasets is included in Section 10. 5.

- a) Does the Division concur with BI's proposal for submitting datasets in SDTM as described above and in Section 10.5?

FDA Pre-Meeting Comments and Question

Clinical:

We agree with the proposal to submit full tabular datasets for study 1275.1 in SDTM format. Laboratory values in this dataset must be submitted in U.S. conventional units along with reference ranges.

Statistical:

It appears acceptable.

Clinical Pharmacology:

Please clarify which datasets will be provided for the phase I studies in SDTM format. At a minimum, we will require the demographics, concentration-time, derived parameters and adverse events datasets, and a define file addressing the layout of these datasets.

BI Pre-Meeting Response to FDA Query:

Clinical Pharmacology: We will provide to the FDA the following domains for the 1245.30 and 1275.3 trials: DM-Demographics, EX-Exposure, DS-Disposition, PC-Pharmacokinetic Concentrations, PP- Pharmacokinetic Parameters, CO-Comment, AE-Adverse Event and the supplemental domains that go with these domains.

Is this proposal acceptable?

BI's proposals are acceptable. BI and FDA agree on these issues.

- b) Does the Division concur with BI's proposal for submitting datasets in ADaM as described above and in Section 10.5?

FDA Pre-Meeting Response

Statistical:

It appears acceptable.

Agreement was reached on this item.

Question 8

Cross-reference will be made to the data presented in the individual empagliflozin and linagliptin NDAs to establish the cardiovascular (CV) safety profile of the empagliflozin + linagliptin FDC. Does the Agency have any comments on BI's proposed approach for evaluating the CV safety profile of the empagliflozin + linagliptin FDC?

FDA Pre-Meeting Comment

Clinical:

In addition to referencing the individual empagliflozin and linagliptin NDA data for cardiovascular safety, analysis of cardiovascular safety of combination therapy should be submitted. This can be done using the safety database from any completed and ongoing trials where combination therapy was administered.

BI response:

The only completed Phase 2/3 study with empagliflozin and linagliptin combination therapy is Study 1275.1, the final report for which will be included in the NDA (52-weeks treatment duration). This report will provide a summary overview of cardiovascular events that occurred in this study.

For the ongoing studies with the combination (1275.9, 1275.10), we propose to provide a listing of patients with cardiovascular events which occurred during the blinded treatment phase of

these studies. For those cases which have been unblinded because they are considered suspected unexpected serious adverse reactions (see also BI response to FDA comments on Question 3b), BI will additionally provide case report forms and narratives. Additional information for any blinded cases will be provided upon request. This information will be updated in the 4-month safety update.

We note that there are only two other studies, both ongoing, that could potentially include empagliflozin and linagliptin combination therapy:

- Study 1245.25, cardiovascular safety study for empagliflozin*
- Study 1245.52, efficacy and safety of empagliflozin as add-on therapy to an oral antidiabetic drug (sulfonylurea, biguanide, thiazolidinedione, alpha glucosidase inhibitor, DPP4 inhibitor, or glinide) in Japanese patients (52 wks treatment duration, number of planned patients with a DPP4 inhibitor = 126)*

In both these studies, the only information being collected is whether or not the patient is taking a DPP4 inhibitor, and not the specific drug included in the class of DPP4 inhibitors. Therefore, we cannot identify additional patients being treated with linagliptin.

Is this proposal acceptable?

FDA finds BI's response acceptable. BI and FDA have reached agreement on this item, including your agreement to provide 52-week data for Study 1275.1 at the time of NDA submission.

Question 9

The ongoing clinical evaluation of safety and efficacy of empagliflozin or of linagliptin has not identified any unusual safety concerns which might necessitate a risk evaluation mitigation strategy (REMS). Based on current information, BI does not believe that a REMS is necessary at the time of the application. BI will continue to evaluate data and consider the need based on our findings and on the Agency's feedback on empagliflozin during NDA review.

Does the Division have any comments on this plan or on the need for a REMS for this product at the time of the application?

FDA Pre-Meeting Response

Division of Risk Management:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Note that BI had no additional comments and agreed with FDA's assessment. Agreement was reached regarding this issue.

Question 10

Section 10.6 provides a listing of all empagliflozin + linagliptin FDC studies generating safety information for FDC after data cut-off for the initial NDA submission, and the proposed content of the 4MSU.

Does the Division have any comments to the proposed plan for the 4MSU?

FDA Pre-Meeting Response

Clinical:

Provide further clarification on how the serious unexpected adverse reactions (SUSARs) will be defined. Narratives and case report forms for events as listed in section 10.4 for the completed studies should also be submitted.

BI response:

As described for narratives and CRFs for the initial NDA (see BI response to FDA comments on Question 3b), for ongoing blinded studies (1275.9 and 1275.10), at the time of the 4MSU, BI expects that most of the cases requested will be unblinded, and narratives and CRFs will be provided. Additionally, BI will provide an updated blinded listing of the requested adverse events for which narratives and CRFs are not provided. Is this proposal acceptable?

FDA finds BI's comments acceptable. Agreement was reached

Regulatory

Question 11

At the time of the NDA submission, BI anticipates requesting a waiver, under 21 CFR Section 314.55, of the requirements for pediatric studies in patients.

Does the Agency have any comment on BI's proposed approach for empagliflozin + linagliptin FDC tablets in type 2 diabetic pediatric population?

FDA Pre-Meeting Response

It is unlikely that a full waiver of the requirement for pediatric study of your proposed fixed dose combination would be granted. The conditions for granting of a full waiver are specified under CFR 314.55(c)(2), and your product does not appear to meet those conditions.

In general, the Division of Metabolism and Endocrinology Products has not granted full waivers of the pediatric study requirement for products intended for the treatment of type 2 diabetes. For some products, a partial waiver has been granted for the study of children ages 0-9 years, under CFR 314.55(c)(2)(i) and CFR 314.55(c)(2)(ii). However, study in children ages 10-17 years has been required for almost all products for the treatment of type 2 diabetes.

If you wish to request a full or partial waiver of the pediatric study requirement, please submit adequate justification under one or more of the conditions cited in CFR 314.55(c)(2).

BI response:

Thank you for your comments.

The Initial Pediatric Study Plan (PSP) for the empagliflozin + linagliptin FDC was submitted to IND 108388 on July 26, 2013. We plan to submit the NDA before January 5, 2014; however, if the NDA is submitted after January 5, 2014, we recognize that the PSP submission date may not meet the requirements of PDUFA V.

Please advise how we would proceed in that situation.

FDA Comments (not previously provided):

We reference the new draft guidance: *Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. As stated in Appendix 1:

“If you submit an NDA, BLA, or efficacy supplement that triggers PREA before January 5, 2014, the FDA intends to exercise enforcement discretion with regard to the new provisions found in FDASIA that require an agreed upon initial PSP be submitted as part of the application. However, the FDA encourages sponsors who are planning to submit such an application before January 5, 2014, to submit an initial PSP for review as soon as possible. Sponsors should be aware that review of, and agreement to an initial PSP generally will require at least 7 months. If an agreed-upon initial PSP is not included in the application, the sponsor should submit a description of the planned or ongoing studies as previously required under PREA.”

If you submit an application after January 5, 2014, failure to include an agreed upon PSP may be a refuse-to-file (RTF) issue.

Question 12

Based on current submission timelines, the empagliflozin + linagliptin FDC NDA will be submitted before the empagliflozin NDA 204629 is approved. Please confirm that the target FDA review period for empagliflozin + linagliptin FDC NDA, based on PDUFA V guidelines, will be 10 months following submission.

FDA Pre-Meeting Response

The empagliflozin / linagliptin FDC NDA will be reviewed under a 12 month clock.

FDA and BI agree on this issue.

If you have any questions, call Patricia Madara at 301-796-1249.

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

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
08/14/2013



IND 108388

MEETING PRELIMINARY COMMENTS

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Lee-Sogaard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for empagliflozin / lingliptin fixed-dose-combination (FDC) tablets.

We also refer to your May 31, 2013, correspondence requesting a preNDA meeting to discuss submission of an NDA for empagliflozin / lingliptin FDC tablets.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: PreNDA

Meeting Date and Time: July 31, 2013; 12 noon
Meeting Location: teleconference

Application Number: IND 108388
Product Name: empagliflozin + linagliptin-fixed-dose combination (FDC) tablets
Indication: treatment of type 2 diabetes
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Introduction

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 31, 2013, between Boehringer Ingelheim and FDA. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. 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.

Background

On June 24, 2011, Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted a new IND for empagliflozin + linagliptin fixed dose combination (FDC) tablets. The proposed indication is use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The company is developing two dosage strengths: empagliflozin 10 mg + linagliptin 5 mg and empagliflozin 25 mg + linagliptin 5 mg.

On May 31, 2013, BI submitted a Type B, preNDA meeting request to IND 108388. The purpose of the meeting was to discuss submission of an NDA for empagliflozin + lingliptin

FDC tablets. The sponsor requested a one hour teleconference and it was granted. The meeting date is July 31, 2013.

Linagliptin (5 mg tablet) was approved on May 2, 2011, under NDA 201280 (tradename – Trajenta) and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Linagliptin (BI 1356) is an orally active dipeptidyl peptidase IV (DPP4) inhibitor. DPP4 degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta-cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in hepatic glucose output. Regulation of incretin hormones in the gut, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), appears to be the primary role of DPP4 in regulating postprandial glucose. DPP4 inhibition by linagliptin prevents the natural rapid breakdown of GLP-1 and GIP after their postprandial expression.

BI submitted an IND to develop empagliflozin (BI 10773) on April 10, 2008. An NDA for empagliflozin, 10 mg and 25 mg tablets, was received on March 5, 2013 and is currently under review. As with linagliptin, the proposed indication for empagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Empagliflozin belongs to a class of drug designed to inhibit sodium-glucose co-transporter 2 (SGLT2) in the kidneys. SGLT2 is predominately located on the luminal side of brush border membrane of proximal tubules in the kidneys with minimal presence in other tissues. Since this transporter is involved in transport of glucose from tubules back to blood, it has been hypothesized that SGLT2 inhibition would prevent glucose reabsorption, leading to increased glucose clearance by the kidneys, resulting in lower blood glucose. Under normal conditions, the kidneys transport nearly all the filtered glucose back into the blood via glucose transporters (i.e. SGLT2). This uptake capacity is saturated at a blood glucose concentration of ~ 180 mg/dl (10 mM), resulting in glucosuria. By inhibiting SGLT2, this threshold is reduced, leading to greater loss of glucose via kidneys.

Empagliflozin is a new molecular entity (NME) and is being reviewed as mandated under the new PDUFA V “Program.” Because the NDA for the combination of empagliflozin + linagliptin is expected to arrive prior to the possible approval of empagliflozin monotherapy, the combination will be considered an NME and will also be reviewed under the “Program.”

Discussion

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1

In Module 3 of the empagliflozin + linagliptin FDC tablets NDA, BI plans to include complete drug product and regional sections (3.2.P and 3.2.R) for empagliflozin + linagliptin FDC tablets. Throughout Module 3, sections where no information is filed will be omitted from the NDA submission per ICH Guidance for Industry M4: The CTD – General Questions and Answers, December 2004. These sections will be identified in both the NDA cover letter and the reviewer's guide. Tentatively, the sections BI will not include are: 3.2.P.3.5 Process Validation and/or Evaluation, and 3.2.P.4.6 Novel Excipients. Section 3.2.P.6 Reference Standards or Materials will also not be included; however, BI will refer to the relevant information in the linagliptin and empagliflozin NDAs, 201280 and 204629, respectively. Additional sections for which no information is filed may be added to this list. The drug substances used for the empagliflozin + linagliptin FDC tablets are (b) (4) described in NDA 204629 for empagliflozin which will be under review, and to the approved NDA 201280 for linagliptin. Therefore, BI plans to refer to the drug substance information in the empagliflozin and linagliptin NDAs and does not plan to include any drug substance documentation in Module 3.2.S of the empagliflozin + linagliptin FDC NDA.

In addition, it is proposed to provide in Module 2 of the empagliflozin + linagliptin FDC NDA a Quality Overall Summary (QOS) which will summarize the new drug product information. A table of contents for Module 3 is provided in Section 10.2.

Does the Division have any comments about the proposed approach for Module 3 and QOS of the empagliflozin + linagliptin FDC NDA?

FDA Response

We agree with your proposed Module 3 sections and QOS of the new NDA. We remind you to include in the NDA a complete list of all testing and manufacturing facilities used for the drug substances and drug product in Form 356h of the NDA, with detailed contact information and a statement that all facilities are ready for the GMP inspection at the time of the NDA submission.

Nonclinical

Question 2

In Module 4 of the empagliflozin + linagliptin FDC NDA, BI plans to include only those nonclinical reports specifically assessing the nonclinical safety of concomitant administration of empagliflozin and linagliptin. A table of contents for Module 4 is provided in Section 10.2. In addition, BI plans to cross-reference reports and datasets previously provided in Module 4 of the empagliflozin NDA and the linagliptin NDA. BI proposes that the new reports for concomitant administration, and nonclinical information cross referenced to the NDAs, will fulfill the requirement of the Nonclinical Summary (Module 2.6); therefore, no additional summary documents are planned to be provided.

- a) Does the Division have any comments regarding the general organization and/or proposed content to be included in Module 4 of the NDA?

FDA Response

We prefer that you also include non-clinical written and tabulated summaries that address the additional studies conducted to support the FDC. It is acceptable to cross-reference the monotherapy NDAs for the other toxicology studies.

- b) Does the Division have any comments on the proposed plan?

FDA Response

The content of Module 4 appears appropriate, but please see the response to question 2a above.

Clinical

The clinical information for the empagliflozin + linagliptin FDC NDA will comprise the final reports of one pivotal Phase III clinical study (1275.1) and two Phase I clinical pharmacology studies in healthy volunteers (1245.30 [drug to drug interaction study] and 1275.3 [relative bioavailability study]). The two Phase I study reports have been previously submitted to NDA 204629 for empagliflozin tablets and to IND 108388 for the empagliflozin + linagliptin FDC. These three reports will make up the totality of clinical information from completed studies using the combination of empagliflozin + linagliptin.

- Study 1275.1: A phase III, randomized, double-blind, parallel group study to evaluate the efficacy of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control (metformin treated: N=665 [planned], N= 684 [actual]; treatment-naïve: N=665 [planned], N= 677[actual])
- Study 1245.30: Relative bioavailability of multiple doses BI 10773 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of BI 10773 50 mg and linagliptin 5 mg administered alone to healthy male volunteers (an open-label, randomised, crossover, clinical phase I study) (N=16)
- Study 1275.3: Relative bioavailability investigations of a 25 mg BI 10773/5 mg linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single dose, crossover, Phase I trial in healthy male and female volunteers) (N=42)

Two additional studies will be ongoing at the time of the NDA submission (Studies 1275.9 and 1275.10). The only data included for these studies will be narratives and CRFs for patients with serious adverse events that qualify for expedited reporting (SUSARs).

- Study 1275.9: A phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.
- Study 1275.10: A phase III, randomized, double-blind, parallel group study to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combination with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks of treatment with empagliflozin 10 mg or 25 mg on metformin background therapy.

A table of contents for Module 5 is provided in Section 10.2.

Question 3

- a) Does the Division have any comments regarding the general organization and/or proposed content to be included in Module 5 of the NDA?

FDA Response

Clinical:

The proposed organization for module 5 appears acceptable.

- b) Does the Division have any comments on the proposed plan?

FDA Response

Clinical:

Please provide your rationale for not submitting the final study reports for studies 1275.9 and 1275.10 at the time of submission of your NDA. Additionally, clarify if there are any other studies not listed in the pre-NDA meeting package where subjects are exposed to the combination of empagliflozin and linagliptin.

Please clarify what is meant when you use the acronym SUSAR. In the “Question” section of the meeting package you state that SUSARs are serious adverse events that qualify for expedited reporting and then in section 10.6 define it as a serious unexpected suspected adverse reaction. In addition, narratives and CRFs as listed for the completed trials in section 10.4 should be submitted for the ongoing studies.

Question 4

The single entity tablets empagliflozin and linagliptin that were used in the pivotal safety and efficacy Study 1275.1 and the relative bioavailability Study 1275.3 are equivalent formulations to the to-be-marketed empagliflozin 10 and 25 mg tablets described in NDA 204629 (submitted March 5, 2013) and to the marketed TRADJENTA 5 mg tablets described in NDA 201280 (approved May 2, 2011). At the start of study 1275.1, the empagliflozin + linagliptin FDC tablets in Study 1275.1 were (b) (4) empagliflozin + linagliptin FDC tablets used in the bioavailability Study 1275.3, which supports equivalence of the FDC to its components. During

the 1275.1 trial, there was a minor change to the quantitative composition of the FDC tablets.

(b) (4)
in the FDC tablets when compared to the FDC tablets used in 1275.3 and first used in trial 1275.1. This change was not deemed to impact the bioavailability of the active components. Considering these data, BI believes that reference to the NDAs for the individual drug products to support safety and efficacy of empagliflozin and linagliptin is appropriate. Does the Division concur with BI's approach?

FDA Response

Biopharmaceutics Response:

This submission did not include a comparative qualitative and quantitative composition of the FDC formulation for the pre- and post change. However, based on the percent change mentioned in the question above, this manufacturing change could be considered minor requiring dissolution profiles comparisons. Therefore, to support the bridging of these formulations, provide the following information in the NDA submission:

- 1. Comparative qualitative and quantitative composition of the FDC formulation for both strengths of your product for the pre- and post change.**
- 2. Comparative dissolution data using the regulatory dissolution method for each FDC tablet strength manufactured pre- and post- the proposed changes. Also, provide individual (n=12), mean, minimum, maximum, RSD, profile data, and calculate the similarity factor f2 values.**

Additional Biopharmaceutics Comments

General comments to consider for information expected at the time you plan to submit your proposed dissolution method:

- 1. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable.**
- 2. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) generated during the method development. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).**
- 3. Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are**

intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

- 4. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e. specification-sampling time point and specification value) for both components of the proposed product.**
- 5. Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

- 6. Per CFR §320.22 and the Guidance for Industry “Bioavailability and Bioequivalence Studies for Orally Administered Drug Product – General Considerations”, the requirement for the submission of evidence measuring the in vivo bioavailability or demonstrating the bioequivalence of the lower strength (10 mg empagliflozin/5 mg linagliptin) can be waived if you submit a biowaiver request and meet the following criteria:**

- The lower strength is [REDACTED] ^{(b) (4)} in its active and inactive ingredients to the higher strength.**
- Dissolution profile comparisons between the highest and lower strengths in three different media meet the f2 similarity requirements.**
- There is BA/BE data for the highest strength.**

Question 5

The pivotal Phase III trial 1275.1 is a 52 week study to evaluate the efficacy and safety of empagliflozin + linagliptin FDC tablets compared to the individual components with primary efficacy analysis at 24 weeks. The final clinical trial report of the 52 week study, which will include the data from the primary analysis at 24 weeks, will be submitted in the NDA. The clinical trial report for the analysis of the data at 24 weeks is currently in preparation; BI is including a summary of the key safety and efficacy results in Section 10.3 and the draft clinical trial report in Module 1.11.3. The study is continuing with blinding in place for all personnel who continue to be involved in the operation and evaluation of the study to week 52.

- a) Do the results for the 24 week primary analysis of 1275.1 support the safety and efficacy for the FDC as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and empagliflozin is appropriate?

FDA Response

Clinical:

We concur that the primary endpoint may be measured at 24 weeks. We prefer that the 52 week information (particularly safety information) also be submitted at the time of the initial fixed dose combination NDA submission. This is because, in distinction to the majority of approved fixed dose combinations for type 2 diabetes, this FDC consists of two very new products: empagliflozin, which is not yet approved at all; and linagliptin, which was only recently approved. Most approved fixed dose combinations include at least one component for which we have a long safety experience, for example combinations with metformin or sulfonylurea.

Statistical:

Your primary analysis uses the LOCF method for dealing with missing data which is no longer recommended by the Division since the publication of a report on missing data by the National Academy of Sciences (NAS, 2010), *The Prevention and Treatment of Missing Data in Clinical Trials*. The report states “The panel believes that in nearly all cases, there are better alternatives to [LOCF]...which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects”. We suggest that you submit an amendment for your Statistical Analysis Plan (SAP) to propose a statistical analysis which does not rely on LOCF and which is in line with NAS recommendations before submitting the NDA.

Question 6

- a) Section 10.4 outlines which case report forms (CRFs) BI proposes to include in the empagliflozin + linagliptin NDA. Does the Division concur with BI’s proposal?

FDA Response

Clinical:

We agree with the proposed list of CRFs to be submitted for the completed trials. CRFs from the ongoing blinded studies should be submitted based on the same list.

- b) Section 10.4 outlines which case narratives BI proposes to include in the empagliflozin + linagliptin NDA. Does the Division concur with BI’s proposal?

FDA Response

Clinical:

We agree with the proposed list of CRFs to be submitted for the completed trials. CRFs from the ongoing blinded studies should be submitted based on the same list. For the proposed hyper-linked table in section 15.4.3 of the clinical study report and in module 5.3.5.1 listing all the subjects with narratives and case report forms, also include the associated MedDRA preferred term(s) and treatment assignment.

Question 7

BI will provide full datasets for the pivotal phase III study 1275.1. BI will provide the datasets developed for the 52-week efficacy and safety analysis only. A sensitivity assessment on the primary efficacy endpoint at 24 weeks will be incorporated additionally into the 52-week clinical trial report in order to demonstrate that potential database updates which followed completion of the 24-week primary analysis had no influence on the results obtained. The tabular datasets will be provided in SDTM and the analysis datasets in ADaM format.

BI will provide limited tabular datasets (SDTM) for the phase I studies in healthy volunteers (Studies 1245.30 and 1275.3).

A full description of the proposal for datasets is included in Section 10. 5.

- a) Does the Division concur with BI's proposal for submitting datasets in SDTM as described above and in Section 10.5?

FDA Response

Clinical:

We agree with the proposal to submit full tabular datasets for study 1275.1 in SDTM format. Laboratory values in this dataset must be submitted in U.S. conventional units along with reference ranges.

Statistical:

It appears acceptable.

Clinical Pharmacology:

Please clarify which datasets will be provided for the phase I studies in SDTM format. At a minimum, we will require the demographics, concentration-time, derived parameters and adverse events datasets, and a define file addressing the layout of these datasets.

- b) Does the Division concur with BI's proposal for submitting datasets in ADaM as described above and in Section 10.5?

FDA Response

Statistical:

It appears acceptable.

Question 8

Cross-reference will be made to the data presented in the individual empagliflozin and linagliptin NDAs to establish the cardiovascular (CV) safety profile of the empagliflozin + linagliptin FDC. Does the Agency have any comments on BI's proposed approach for evaluating the CV safety profile of the empagliflozin + linagliptin FDC?

FDA Response

Clinical:

In addition to referencing the individual empagliflozin and linagliptin NDA data for cardiovascular safety, analysis of cardiovascular safety of combination therapy should be submitted. This can be done using the safety database from any completed and ongoing trials where combination therapy was administered.

Question 9

The ongoing clinical evaluation of safety and efficacy of empagliflozin or of linagliptin has not identified any unusual safety concerns which might necessitate a risk evaluation mitigation strategy (REMS). Based on current information, BI does not believe that a REMS is necessary at the time of the application. BI will continue to evaluate data and consider the need based on our findings and on the Agency's feedback on empagliflozin during NDA review.

Does the Division have any comments on this plan or on the need for a REMS for this product at the time of the application?

FDA Response

Division of Risk Management:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Question 10

Section 10.6 provides a listing of all empagliflozin + linagliptin FDC studies generating safety information for FDC after data cut-off for the initial NDA submission, and the proposed content of the 4MSU.

Does the Division have any comments to the proposed plan for the 4MSU?

FDA Response

Clinical:

Provide further clarification on how the serious unexpected adverse reactions (SUSARs) will be defined. Narratives and case report forms for events as listed in section 10.4 for the completed studies should also be submitted.

Regulatory

Question 11

At the time of the NDA submission, BI anticipates requesting a waiver, under 21 CFR Section 314.55, of the requirements for pediatric studies in patients.

Does the Agency have any comment on BI's proposed approach for empagliflozin + linagliptin FDC tablets in type 2 diabetic pediatric population?

FDA Response

It is unlikely that a full waiver of the requirement for pediatric study of your proposed fixed dose combination would be granted. The conditions for granting of a full waiver are specified under CFR 314.55(c)(2), and your product does not appear to meet those conditions.

In general, the Division of Metabolism and Endocrinology Products has not granted full waivers of the pediatric study requirement for products intended for the treatment of type 2 diabetes. For some products, a partial waiver has been granted for the study of children ages 0-9 years, under CFR 314.55(c)(2)(i) and CFR 314.55(c)(2)(ii). However, study in children ages 10-17 years has been required for almost all products for the treatment of type 2 diabetes.

If you wish to request a full or partial waiver of the pediatric study requirement, please submit adequate justification under one or more of the conditions cited in CFR 314.55(c)(2).

Question 12

Based on current submission timelines, the empagliflozin + linagliptin FDC NDA will be submitted before the empagliflozin NDA 204629 is approved. Please confirm that the target FDA review period for empagliflozin + linagliptin FDC NDA, based on PDUFA V guidelines, will be 10 months following submission.

FDA Response

The empagliflozin+linagliptin FDC NDA will be reviewed under a 12 month clock.

ADDITIONAL IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 14, 2013, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) no later than 60 days after an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

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

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

INFORMATION REQUESTS FROM THE OFFICE OF SCIENTIFIC INVESTIGATION

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format).

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

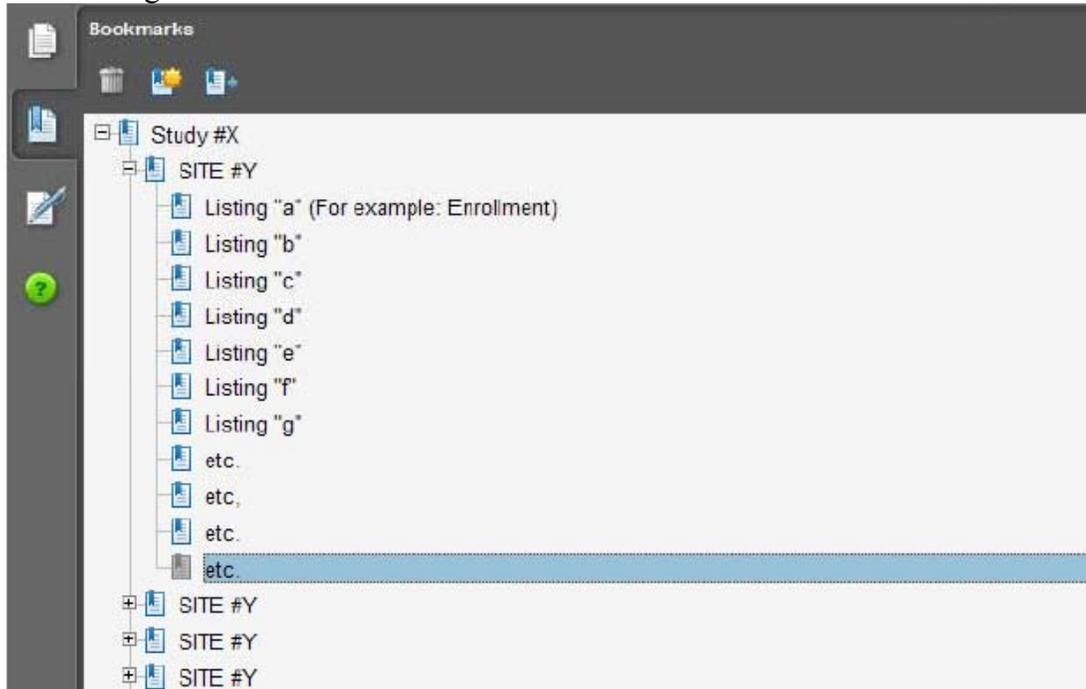
1. Please include the following information in a tabular format in the original NDA/BLA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal Investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)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

- b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued at each site
3. Please include the following information in a tabular format in the NDA/BLA for each of the completed pivotal clinical trials:
- a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described in ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all contract research organizations (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571) you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated case report form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial, provide the original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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



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

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

IND 108388
Preliminary Meeting Comments

References:

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

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

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

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/s/

PATRICIA J MADARA
07/29/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 108388

MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your Pre-Investigational New Drug Application (PIND) for linagliptin and BI 10773 fixed-dose combination.

We also refer to the teleconference held between representatives of your firm and the FDA on July 28, 2010. The purpose of this End-of-Phase 2 meeting was to discuss your plans to submit an IND for linagliptin and BI 10773 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) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Consumer Safety Officer
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Phase 2 Meeting Minutes

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: July 28, 2010, 3:00 PM – 3:15 PM (Eastern)
Meeting Location: Teleconference

Application Number: 108388
Product Name: Linagliptin and BI 10773 fixed-dose combination
Indication: Treatment of Type 2 Diabetes Mellitus

Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Raymond Chiang, M.S.

FDA ATTENDEES

Office of Drug Evaluation II

Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Hylton Joffe, M.D.	Diabetes Team Leader, DMEP
Ilan Irony, M.D.	Diabetes Team Leader, DMEP
Lisa Yanoff, M.D.	Clinical Reviewer, DMEP
Somya Dunn, M.D.	Clinical Reviewer, DMEP
David Carlson, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Lina AlJuburi, Pharm.D.	Chief, Project Management Staff, DMEP
Raymond Chiang, M.S.	Consumer Safety Officer, DMEP

Office of Biometrics

Lee Ping Pian, Ph.D.	Statistics Reviewer, Division of Biometrics II (DBII)
Jon T. Sahlroot, Ph.D.	Deputy Director and Statistics Team Leader, DBII

Office of Clinical Pharmacology

Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Reviewer, DCP2
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SPONSOR ATTENDEES

Dan Coleman, Ph.D.	Associate Director, Regulatory Affairs
David Hall, Ph.D.	Project Statistician
Kathryn Jason, Ph.D.	Director, Regulatory Affairs

Dacheng Liu, Ph.D.
Angelina Trujillo, M.D.

Project Statistician
Senior Associate Director, Clinical Research

1.0 BACKGROUND

On April 1, 2010, Boehringer Ingelheim Pharmaceuticals, Inc. submitted a Type B End-of-Phase 2 meeting request to discuss their drug development program for linagliptin and BI 10773 fixed-dose combination. The meeting briefing package was submitted on June 17, 2010. The NDA is not planned to be filed until both linagliptin and BI 10773 are approved to be marketed for type 2 diabetes mellitus.

Linagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4). The sponsor submitted the IND (IND 70963) for linagliptin on August 19, 2005. The original NDA (NDA 201280) for linagliptin was submitted on July 2, 2010, for the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

BI 10773 is an inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2). For BI 10773 Phase 2 trials have been completed and Phase 3 trials are planned to be initiated under IND 102145, which was submitted on April 10, 2008.

According to the meeting briefing package, the sponsor is proposing to conduct the following pivotal study 1275.1 for safety and efficacy of linagliptin and BI 10773 fixed-dose combination: “A randomised, double-blind, parallel group efficacy and safety study of Linagliptin 5mg + BI 10773 25 mg and of Linagliptin 5mg + BI 10773 10 mg Fixed Dose Combination Tablets (administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycemic control ($HbA1c \geq 7.0 \leq 10\%$) with or without a background of metformin therapy (≥ 1500 mg per day).”

2.0 DISCUSSION

NOTE: The Sponsor requested discussion and responses to the following questions. The questions are repeated below and the Division’s preliminary responses provided to the sponsor on July 26, 2010, follow in **bold** font. A summary of the meeting discussion is shown in underlined text.

2.1 NonClinical:

Question 1: Does FDA agree with the proposed design and dose selection for the 13-week rat toxicology study with linagliptin and BI 10773 included as Item 10.3?

FDA Preliminary Response: **The proposed protocol includes appropriate control and treatment groups to assess toxicological effects of combined linagliptin + BI 10773 treatment in rats. Lists of clinical pathology and necropsy investigations were not included in Appendices 1 and 2. The Division recommends collection and analysis of a complete battery of clinical pathology, tissues/organs for necropsy, and organ weights in accordance**

with standard practice for GLP rat toxicity studies. In addition, the Division continues to recommend monitoring nonclinical exploratory kidney biomarkers and bone biomarkers as previously communicated for BI 10773 in IND 102,145.

Meeting discussion: None

Question 2: Will the nonclinical data from the monotherapy programs (see Item 10.1 and 2), together with the 13-week rat study with linagliptin and BI 10773 (see Item 10.3), be sufficient nonclinical information to support filing a New Drug Application for the FDC?

FDA Preliminary Response: The Division requests that the sponsor conduct an embryofetal reproductive toxicology study (Segment 2 study) with the linagliptin plus BI 10773 combination in rats. The Division recommends the combination embryofetal development study include separate linagliptin and BI 10773 arms in addition to the combination groups (similar to your 13-week rat combination toxicity protocol). Adequacy of materials to support filing will be a review issue upon NDA submission.

Meeting discussion: None

2.2 Biopharmaceutics and Clinical Pharmacology:

Question 3: Does FDA agree that the following clinical pharmacology and biopharmaceutics data will be sufficient to support filing a New Drug Application for the FDC?

Clinical Pharmacology Program:

- 1) The completed and proposed clinical pharmacology and biopharmaceutics studies from the development programs of the single drug formulations, linagliptin and BI* 10773, respectively (listed in Item 10.4 and described in Item 10.1 and 10.2)?
- 2) The relative bioavailability study (1275, see Item 10.6) which
 - a) compares the FDC (linagliptin 5mg/BI 10773 25 mg) with the combined administration of the two individual drug formulations (linagliptin 5 mg and BI 10773 25 mg)
 - b) investigates the effect of food on the bioavailability of the FDC
- 3) A drug-drug interaction study (1245.30, see Item 10.5), comparing the relative bioavailabilities of linagliptin and BI 10773 when given either alone or in combination.

FDA Preliminary Response: The planned studies with the FDC seem adequate.

Additional comments:

- **You are proposing two strengths (5 mg/10 mg and 5 mg/25 mg) for the linagliptin/BI 10773 FDC. The adequacy of these proposed doses for the FDC will depend on the acceptability of the doses for the individual drugs, which is not certain until after we have completed our reviews of the linagliptin and BI 10773 NDAs.**

- **Many of the Clinical Pharmacology studies for BI 10773 including the DDI study (1245.3) between linagliptin and BI 10773 have been conducted only in males. We recommend that you characterize the effect of gender on the pharmacokinetics (PK) of both linagliptin and BI 10773.**

Meeting discussion: None

Question 4: Does the FDA agree that the design of study 1275.3 (see Item 10.6) is appropriate to support labeling to allow patients to switch from the free combination to the FDC?

FDA Preliminary Response: The design of study 1275.3 is acceptable in evaluating relative bioavailability and food effect for the FDC. However, the labeling information will be a review issue.

Meeting discussion: None

2.3 Clinical:

Question 5: Does FDA concur that the proposed Phase 3 study 1275.1 (see Item 10.7) can begin prior to completion of the 13-week rat toxicology study?

FDA Preliminary Response: No. There is currently inadequate clinical experience with the coadministration of linagliptin and BI 10773 to support initiation of this phase 3 trial prior to completion of the toxicology study.

Meeting discussion: None

Question 6: Does FDA concur that the clinical development of this FDC may begin prior to the approval to market either of the individual components?

FDA Preliminary Response: Yes, provided that the appropriate studies are completed to support your phase 3 trial (see response to Question 5).

We recommend that your relative bioavailability study (1275) be completed prior to initiation of the Phase 3 study 1275.1. If you only conduct the relative bioavailability study after the phase 3 study is underway and you subsequently find that the FDC product used in your Phase 3 study 1275.1 is not bioequivalent to coadministration of the individual components, further clinical studies may be necessary. For example, if your FDC formulation results in a substantially increased pharmacokinetic exposure to linagliptin and/or BI 10773, we will have limited safety data at these exposures from the individual NDAs to support your FDC.

Meeting discussion: None

Question 7: Does FDA concur with the sponsor's plan for clinical development, and that the Phase 3 study design of Study 1275.1 (see Items 10.7 and 10.8) is adequate to support the proposed indication for the FDC?

FDA Preliminary Response: Based on our review of your protocol synopses, the studies appear to be adequate to support the proposed indication for the FDC except where discussed in our other responses. However, the exact wording of the indication will be a review issue. In addition, we may have additional comments on the protocol designs after you have submitted the full protocols for review.

Meeting discussion: None

Question 8: Does FDA concur with the Statistical Analysis Plan (SAP) proposed for the 1275.1 study (see Item 10.8), in particular, the strategy of separate type one error control and conducting the statistical analyses based on a primary analysis of two separate sub-populations?

FDA Preliminary Response: Testing separately powered sub-populations (add-on metformin, and naïve) is fine. Within each subpopulation the combination rule should apply, that is, each combination dose should be shown to be superior to the respective components at the same dose. These tests are simultaneous and, therefore, not equivalent to sequential tests.

Meeting discussion: The Division stated that each combination dose (i.e. BI 10773 25mg/linagliptin 5mg and BI 10773 10 mg/linagliptin 5mg) should be shown superior to the respective components simultaneously, not sequentially. Referring to the sponsor's July 26, 2010 email, the Division stated that pair 1 and 2 must simultaneously demonstrate, with a 5% alpha, superiority to each respective component. If the results for pair 1 and 2 are significant, then pair 3 and 4 may be analyzed. Pair 3 and 4 must also simultaneously demonstrate, with 5% alpha, superiority to each respective component. The sponsor verbalized understanding and had no more comments.

Question 9: Does FDA concur that exposure to treatment with the linagliptin/BI 10773 FDC in the proposed trials will be adequate to support a New Drug Application for this FDC?

FDA Preliminary Response: We cannot concur on the adequacy of exposure numbers at this time. In the Phase 3 trial, there will be 1300 randomized patients. However, only 520 patients will be exposed to the combination product, and only 260 will be exposed to the high-dose combination. Exposure requirements to establish safety will be a review issue, and will depend on any safety signals that emerge during your development program for the FDC and during the development programs for the individual drugs.

Meeting discussion: None

Question 10: Does the FDA have any general comments regarding the clinical development program?

FDA Preliminary Response: Please confirm that the run-in period for submaximal/maximal doses of metformin background therapy is of sufficient duration for the phase 3 protocol to ensure that glycemic control is accurately reflected in the baseline HbA1c measurement.

Please specify stable background therapy (no change during trial) in the protocol.

We recommend that you collect sparse PK samples from the patients or subset of patients at each dose level in the Phase 3 trial (1275.1) to obtain pharmacokinetic information of the FDC that can be used in population PK/PD analysis.

We note that several of your questions ask whether your proposal will support filing of an NDA for the FDC. While your proposal (with the caveats described in our responses) appears reasonable for developing your FDC based on available information to date, a decision on whether the NDA will be filed will be a review issue made after the NDA is submitted.

Meeting discussion: None

Regulatory:

Question 11: Does FDA concur that in this IND (108388) for the FDC, BI may refer to IND 70963 for linagliptin and IND 102145 for BI 10733 for all information regarding the individual components?

FDA Preliminary Response: In addition to the individual INDs, you should also refer to your pending NDA 201280 for linagliptin tablets.

Meeting discussion: None

Question 12: Does FDA concur that the existing INDs for the individual components should refer to the new FDC IND for all information regarding this specific FDC; and reports for the combination will only be submitted to the FDC IND?

FDA Preliminary Response: No. Serious and unexpected adverse event (AE) reports submitted to this FDC IND should also be submitted to the individual components' INDs. One cover letter listing all relevant INDs, which is then submitted to all the relevant INDs, is acceptable.

Meeting discussion: None

4.0 ACTION ITEMS

No action items for the meeting minutes.

5.0 ATTACHMENTS AND HANDOUTS

The sponsor emailed response to FDA preliminary comments provided to sponsor on July 26, 2010.

From: daniel.coleman@boehringer-ingenelheim.com
To: [Chiang, Raymond](#);
Subject: BI response to FDA preliminary comments
Date: Tuesday, July 27, 2010 4:08:53 PM

Dear Ray,

Thank you for the preliminary comments to our meeting questions.

We feel that, with one exception, the responses adequately address our questions.

As described in 10.8, Statistical Analysis Plan, we have proposed hierarchical testing within each sub population (+/- metformin).

The hierarchical testing consists of:

1. Superiority of BI 10773 25mg/Lina 5mg versus Lina 5mg
2. Superiority of BI 10773 25mg/Lina 5mg versus BI 10773 25mg
3. Superiority of BI 10773 10mg/Lina 5mg versus Lina 5mg
4. Superiority of BI 10773 10mg/Lina 5mg versus BI 10773 10mg

In response to Question 8, you state that “these tests are simultaneous and, therefore, not equivalent to sequential tests”.

Please clarify whether you are referring to all four tests, or to each pair of tests (1 and 2, or 3 and 4).

If you are referring to all four tests, please clarify if multiplicity adjustments would be necessary.

We would like to discuss this briefly as a teleconference during the originally scheduled time for the meeting.

I will follow up with you regarding the call in information for the teleconference.

Best regards,

Dan

Daniel T. Coleman, Ph.D.
Senior Associate. Director,

Drug Regulatory Affairs

Office Phone: (203) 798-5081

Office Fax: (203) 791-6262

E-mail: daniel.coleman@boehringer-ingenelheim.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-108388	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	BI-10773/linagliptin-FDC Fixed Dose Combination Tablets

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/s/

RAYMOND S CHIANG
08/05/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206073

LATE-CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs, BIPI
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Lee-Sogaard:

Please refer to your New Drug Application (NDA) dated January 29, 2014, received January 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for empagliflozin and linagliptin tablets; 10 mg/5 mg and 25 mg/5 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 30, 2014.

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

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 30, 2014 12:00pm- 1:00pm
Meeting Location: Teleconference

Application Number: 206073
Product Name: empagliflozin and linagliptin tablets
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Meeting Chair: William Chong
Meeting Recorder: Callie Cappel-Lynch

FDA ATTENDEES

Jean-Marc Guettier, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
William Chong, M.D.	Clinical Team Leader, Acting, DMEP
Julie Van der Waag, M.P.H.	Chief Project Management Staff, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
David Carlson, Ph.D.	Non-clinical Reviewer, DMEP
Martin White, M.S.	Regulatory Project Manager, DMEP
Michael White, Ph.D.	Regulatory Project Manager, DMEP
Marisa Petruccelli	Regulatory Project Manager, DMEP
Manoj Khurana, Ph.D.	Team Leader, Acting, Office of Clinical Pharmacology (OCP)
Sury Sista, Ph.D.	Reviewer, OCP
Ruthann Davi, Ph.D.	Deputy Director, Division of Biometrics II (DBII)
Jennifer Clark, Ph.D.	Reviewer, DBII
Cynthia Kleppinger, M.D.	Medical Officer, Office of Scientific Investigations (OSI)
Amarilys Vega, M.D.	Medical Officer, Division of Risk Management (DRISK)
Neil Vora, Pharm.D.	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim Independent Assessor

APPLICANT ATTENDEES

Heidi Reidies	US Regulatory
Kathryn Jason	US Regulatory
Jan-Markus Wolters	International Project Leader
Sven Kohler	Pharmacovigilance
Gabriel Kim	Pharmacovigilance
Caroline Lippert	Translational Medicine

Arno Kalkuhl	Non-clinical
James Segretario	US CMC Regulatory
Daniel Cocozza	Data Management
Dacheng Liu	Statistics
Michael Shear	Statistics
Renee Kaste	Clinical Operations
Joerg Pfeifer	Regulatory (Lilly)
Sanjay Patel	Medical Lead
Uli Broedl	Associate Therapeutic Area Head
Martin Larbig	Medical
Amy Patel	Regulatory Observer
Fernando Solimando	Pharmacovigilance
Jens Kraemer	Regulatory
Paul Bispham	Regulatory
Christopher Lee	Medical Affairs
Gerald Waechter	CMC
Joachim Troost	Regulatory Observer
Anette Brunner-Schwarz	R&D Project Manager
Chung Lee-Sogaard	US Regulatory Product Manager

1.0 BACKGROUND

NDA 206073 was submitted on January 29, 2014, and received on January 30, 2014 for empagliflozin and linagliptin tablets.

Proposed indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

PDUFA goal date: January 30, 2015

FDA issued a Background Package in preparation for this meeting on October 17, 2014.

2.0 DISCUSSION

1. Introductory Comments

Discussion: The applicant was advised that the purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. They were also advised that we may not be prepared to discuss any new information submitted in response to the issues identified in the Late Cycle Meeting background package prior to this LCM.

FDA participants were introduced, followed by introduction of the Eastern Research Group participants and sponsor participants.

Discussion of Substantive Review Issues

Discussion: The FDA opened discussion reiterating the efficacy concern communicated in the background package. The FDA stated that they were continuing to consider the efficacy of the empagliflozin/linagliptin 25/5 dose in the treatment naïve population and were reviewing the responses provided by the applicant. Following this, the applicant was provided the opportunity to present and discuss their response. The applicant acknowledged the efficacy finding and discussed the additional exploratory analyses done in an effort to identify a possible cause for this finding. No evident imbalances were seen that might explain the finding. [REDACTED] (b) (4)

Additionally, though the statistical testing stopped prior to testing the empagliflozin/linagliptin 10/5 dose in the treatment naïve population, it was better than the individual components. No additional questions were asked by the FDA, and the applicant was informed that the FDA would continue to consider the application.

2. Additional Applicant Data

Discussion: Additional exploratory analyses were briefly presented by the applicant. No clear reason for the lack of efficacy was identified from these analyses.

3. Review Plans

Discussion: The PDUFA goal date was stated. The applicant asked when they would receive the next round of labeling comments. FDA responded that we are continuing to consider the data in the application and cannot provide a date at this time for when the FDA would be prepared to send meaningful labeling comments.

4. Wrap-up and Action Items

Discussion: There were no action items.

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

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/s/

JEAN-MARC P GUETTIER
11/21/2014



NDA 206073

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Chung Lee-Sogaard, Ph.D.
Associate Director, Regulatory Affairs, BIPI
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Lee-Sogaard:

Please refer to your New Drug Application (NDA) dated January 29, 2014, received January 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for empagliflozin and linagliptin tablets; 10 mg/5 mg and 25 mg/5 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 30, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 30, 2014 12:00pm- 1:00pm
Meeting Location: White Oak Building 22 Room 1315

Application Number: 206073
Product Name: empagliflozin and linagliptin tablets
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

INTRODUCTION

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

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

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date.

Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical: We have concerns with regard to the evidence for efficacy of the combination over the individual products. In particular, the efficacy findings from the treatment naïve population remain puzzling and troublesome. Our review of the data has thus far been unable to provide an explanation for the failure of the 25 mg/5 mg fixed-dose combination (FDC) to demonstrate efficacy above what was seen for empagliflozin 25 mg alone. We

would be interested in hearing your perspective on this and any potential explanation for this finding. As you are aware per 21 CFR 300.50 you should demonstrate that each component of the combination contributes to the claimed effect and you have not for the 25mg/5mg combination.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 15 minutes
Each issue will be introduced by FDA and followed by a discussion.
 - i. Clinical: Evidence for efficacy
3. Additional Applicant Data – 15 minutes (Applicant)
4. Review Plans – 5 minutes
PDUFA date: January 30, 2015
Labeling PMR/PMC date: Preliminary labeling and PMR/PMC comments were sent on October 10, 2014.
5. Wrap-up and Action Items – 5 minutes

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

/s/

JEAN-MARC P GUETTIER
10/17/2014