CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212614Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122138

**MEETING REQUEST-
WRITTEN RESPONSES**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Renee Zindell, M.S., RAC
Associate Director, Regulatory Affairs
900 Ridgebury Road; P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Zindell:

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, and metformin hydrochloride extended-release fixed dose combination tablets.

We also refer to your submission dated December 6, 2017, containing a meeting request. The purpose of the requested meeting was to discuss the format and content of a complete New Drug Application (NDA) which you intend to submit for empagliflozin, linagliptin, and metformin hydrochloride extended-release fixed dose combination tablets.

Further reference is made to our Meeting Granted letter dated December 13, 2017, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 20, 2017, background package.

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, M.D.
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Written Responses

Reference ID: 4552196

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	B
Meeting Category:	Pre-NDA
Application Number:	IND 122138
Product Name:	empagliflozin, linagliptin, and metformin hydrochloride extended-release fixed dose combination tablets
Indication:	as an adjunct to diet and exercise (b) (4) in adults with type 2 diabetes (b) (4)
Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) is developing a triple fixed dose combination (FDC) product of empagliflozin, linagliptin, and metformin hydrochloride (HCl) as an adjunct to diet and exercise (b) (4) in adults with type 2 diabetes (b) (4). BI is the New Drug Application (NDA) holder for Jardiance (empagliflozin) tablets (NDA 204629 approved August 1, 2014) and Glyxambi (empagliflozin and linagliptin) tablets (NDA 206073 approved January 30, 2015). BI states that it has obtained a right of reference and full access to utilize all information included within the approved NDA 021748 for Glumetza (metformin hydrochloride extended-release) tablets.

BI states that its planned NDA for its triple FDC product is comparable to two of its approved metformin hydrochloride extended-release products: NDA 208026 Jentadueto XR (linagliptin and metformin hydrochloride extended-release) tablets (approved on May 27, 2016) and NDA 208658 Synjardy XR (empagliflozin and metformin hydrochloride extended-release) tablets (approved on December 9, 2016).

BI submitted a pre-Investigational New Drug (Pre-IND) meeting request on December 12, 2014, to which the FDA issue written responses on February 26, 2015. In the FDA's written response, it suggested that once BI opened an Investigational New Drug (IND) application for the triple FDC product, further discussion would be useful on BI's proposed approach to support the product's registration.

BI submitted their IND on March 16, 2016, for which no hold comments were communicated during the 30-day Safety Review by the FDA. On April 18, 2016, BI submitted a request for a Type C guidance meeting to discuss the clinical development strategy for their triple FDC product. Written responses were provided on June 14, 2016, with a follow-up communication provided on November 3, 2016.

On December 6, 2017, BI submitted a request for a written-response, pre-NDA meeting to discuss the format and content of a complete NDA for its triple FDC product. FDA granted the meeting on December 13, 2017, and received the meeting background package on December 20, 2017.

2.0 QUESTIONS AND RESPONSES

The sponsor's questions are repeated below in regular text, followed by the FDA response (**bolded**).

2.1. CMC

Question 1: Does the Division have any comments about the general organization and/or proposed content to be included in Module 3 of the NDA?

FDA Response to Question 1:
Your proposed Module 3 content is acceptable for our filing review of the NDA, provided that FDA finds the proposed dosage strengths appropriate for the clinical indication(s) and dosing regimen (dose, frequency, and duration). Comments, if any, regarding specific information in the application will be conveyed to you after our in-depth evaluation.

2.2. Nonclinical

Question 2: Does the Division concur with the proposed nonclinical content to be included in Module 2 and 4 of the NDA?

FDA Response to Question 2:
Yes, we agree that your plan to submit a Nonclinical Overview and the combination toxicity study report and to cross-reference other nonclinical materials is acceptable for filing the NDA.

2.3. Clinical

Question 3: Does the Division concur with the proposed clinical content to be included in Module 2 and 5 of the NDA?

FDA Response to Question 3:
We note that you plan to submit SDTM raw datasets and don't plan to provide ADAM datasets or SAS programs. However, the availability of ADAM datasets and SAS programs at the time of NDA submission facilitates comprehensive and timely review of the submission, avoiding any post-submission information requests. We suggest that you include all ADAM datasets and SAS programs for phase I studies 1361.1 and 1361.3 in Module 5 of the original NDA. Additionally, include 'Summary of Biopharmaceutic Studies and Associated Analytical Methods' (2.7.1) and 'Summary of Clinical Pharmacology Studies' (2.7.2) in Module 2.7 of the NDA and the corresponding analytical validation and quantitation reports and/or any cross-references in section 5.3.

See also our response in Question 4 for additional comments on the clinical data to include in your proposed NDA submission.

Question 4: Does the Division agree that the clinical trial reports and datasets for these supportive studies (Studies 1275.9 and 1275.10) (b) (4)?

FDA Response to Question 4:
Based on the description of studies 1275.9 and 1275.10 it appears that these studies provide additional data (both in terms of efficacy and safety) on the concomitant use of the three drug products. As they have not been previously reviewed by the FDA, you will need to submit the respective clinical trial reports and datasets at the time of the NDA submission. As the study designs are different, it would be reasonable to not pool the three studies.

Discussion of the efficacy and safety from these trials should also be included in the module 2 summaries. Laboratory parameters and analyses must be submitted in US units.

Question 5: Does the Agency concur with the proposed content for the 4MSU?

FDA Response to Question 5:
Yes, we agree with the proposed 4MSU content (i.e., new safety information identified based on review of post-marketing cases reported for concomitant use of linagliptin, empagliflozin, and metformin).

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item 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 submission in the format described, the Applicant can describe location or provide a link 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 submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA 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 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 for each site by site

3. Please include the following information in a tabular format in the NDA 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 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 Organization (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.

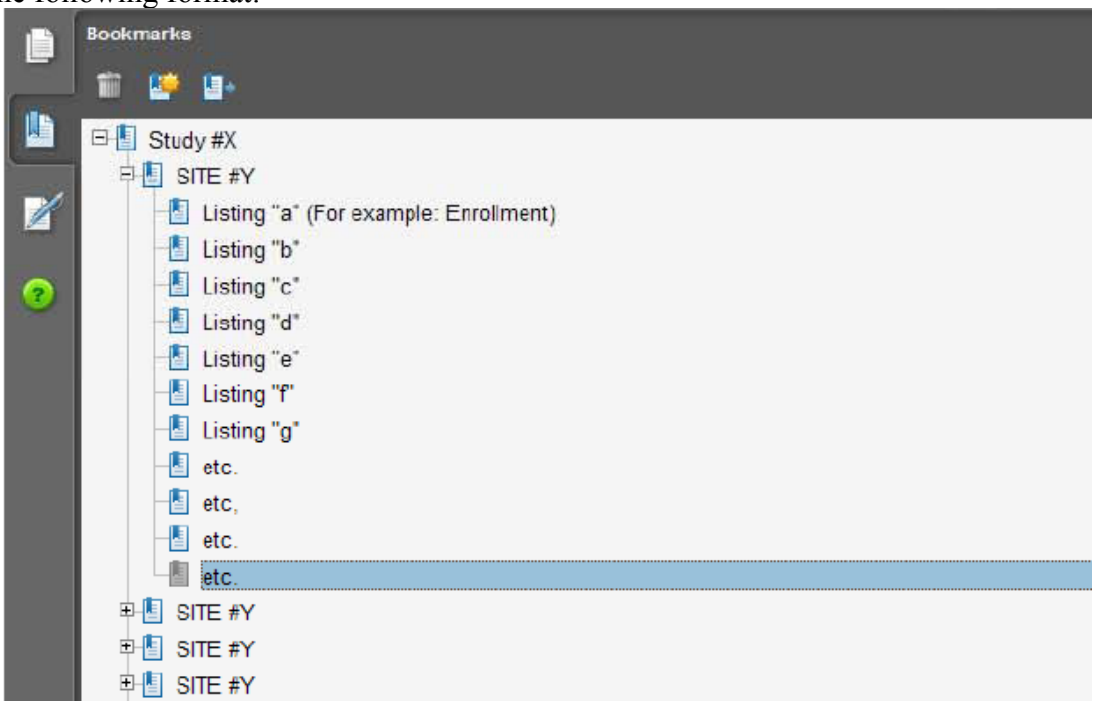
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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 line listings for:
   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, 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

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

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

/s/

MARY T THANH HAI
01/25/2018