

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209091Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

AstraZeneca
Attention: Barbara J. Blandin
Director, Regulatory Affairs
1800 Concord Pike
P O Box 8355
Wilmington, DE 19803-8355

Dear Ms. Blandin:

Please refer to your Pre-Investigational New Drug Application (PIND) file for saxagliptin and dapagliflozin tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 23, 2014. The purpose of the meeting was to discuss the format and content of your planned NDA.

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

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 23, 2014, from 12:00 to 1:30 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22; Conference Room # 1311
Silver Spring, MD 20903

Application Number: IND 118840
Product Name: saxagliptin and dapagliflozin tablets
Indication: Treatment of adults with Type 2 Diabetes Mellitus (T2DM)
Sponsor/Applicant Name: AstraZeneca AB

Meeting Chair: Jean-Marc Guettier, MD
Meeting Recorder: Abolade (Bola) Adeolu, RPh, MS, MBA

FDA ATTENDEES

Jean-Marc Guettier, MD – Director, DMEP
William Chong, MD – Clinical Team Lead (Acting)/Clinical Reviewer
Fred Alavi, PhD - Nonclinical Reviewer
Vikram Sinha, PhD – Director, Division of Pharmacometrics, Office of Clinical Pharmacology
Nitin Mehrotra, PhD – Team Lead, Division of Pharmacometrics
Lokesh Jain, PhD - Clinical Pharmacology Team Lead
Johnny Lau, PhD - Clinical Pharmacology Reviewer
Brad McEvoy, PhD- Statistical Reviewer, Division of Biometrics II (DBII)
Anna Kettermann, PhD - Statistical Reviewer, DBII
Assadollah Noory, PhD- Biopharmaceutics Reviewer
Cynthia Kleppinger, MD- Senior Medical Officer, Office of Scientific Investigations
Rosemary Addy, MS – Supervisory Consumer Safety Officer, Pediatric and Maternal Health Staff (PMHS)
Cynthia Kleppinger, MD- Senior Medical Officer,
Carolyn Yancey, MD- Medical Officer, Division of Risk Management, Office of Surveillance and Epidemiology (OSE)
Julie Marchick, MPH- Chief, Project Management Staff
Abolade (Bola) Adeolu, RPh, MS, MBA

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim- Independent Assessor

SPONSOR ATTENDEES

AstraZeneca

Elisabeth Björk, MD, PhD, VP, Head of CVMD, Global Medicines Development (via telecom)

Barbara Blandin, Regulatory Affairs Director

Sandy Fitt, Director, Clinical Delivery

Boaz Hirshberg, MD, Executive Director, Clinical Research

Ian Hunt, VP, Global Regulatory Affairs, CV/GI TA

John Monyak, Principal Statistician

Artist Parker, MD, Senior Safety Medical Director

Briggs Morrison, EVP Global Medicines Development & Chief Medical Officer

Gerard O'Malley, Global Product VP

Artist Parker, MD, Senior Safety Medical Director

Frank Senk , Programming Team Leader

Donald Stanski, Global Head Quantitative Clinical Pharmacology

(b) (4) Statistical Consultant to AstraZeneca

Bristol-Myers Squibb

Anne Marie Apanovitch, Ph.D, Associate Director, Global Biometric Sciences

David W. Boulton, PhD, Group Director, Clinical Pharmacology & Pharmacometrics

Nayyar Iqbal, MD, Executive Director, Global Clinical Research

Sekayi Mushonga, Pharm.D, Director, Global Regulatory Sciences

1.0 BACKGROUND

A type B meeting request for saxagliptin and dapagliflozin tablets was submitted on April 25, 2014. A teleconference meeting was initially granted and then changed to a face-to-face meeting scheduled for June 23, 2014. AstraZeneca AB is requesting feedback on the format and content of their planned NDA application.

2.0 DISCUSSION

Your questions are repeated below followed by our initial responses in **bold** regular font, then the meeting discussion in *italics*. Post meeting comments are in underlined regular font

Nonclinical Questions

Question 1

The nonclinical profiles of saxagliptin and dapagliflozin have been previously established in a comprehensive development program that included studies of in vitro and in vivo pharmacodynamics (PD), including core safety pharmacology, pharmacokinetics (PK) and metabolism, and toxicity and toxicokinetics (saxagliptin, NDA 22-350 and dapagliflozin, NDA 202-293). In support of the saxagliptin/dapagliflozin FDC product (BMS-986098), an additional 3-month repeated-dose oral combination toxicity study with saxagliptin and dapagliflozin was conducted in rats, and will be included in the NDA. In addition, Modules 2.4, 2.6 and 2.7 will be

submitted in the NDA. No additional nonclinical studies are ongoing or planned to support the saxagliptin/dapagliflozin NDA.

Does the Agency agree that the combination toxicology study is sufficient to support the filing and potential approval of the saxagliptin/dapagliflozin FDC NDA?

FDA Response:

We agree that the 3-month combination toxicology study is sufficient to support the filing and review of the nonclinical components of the NDA.

Meeting Discussion: There was no discussion on this question at the meeting.

Biopharmaceutics/Clinical Pharmacology Questions

Question 2

An ongoing bioequivalence (BE) study (CV181341) comparing the BMS-986098 FDC (b) (4) 5-mg/10-mg BMS-986098 FDC tablets with the respective strengths of saxagliptin and dapagliflozin concomitantly administered in fasted healthy adults will be completed and submitted as part of the NDA. In the Agency's written response to the Sponsor's pre-IND Meeting request (correspondence dated 5-Aug-2013), the Agency had agreed to the Sponsor's proposal (b) (4)

The NDA application will include the biowaiver request and the complete information supporting the BE waiver request. In addition, supportive of the coadministration of saxagliptin and dapagliflozin in a fixed-dose form is a completed drug-drug interaction study (CV181191) to assess the effect of either agent on the PK of the other agent.

Does the Agency agree that the Clinical Pharmacology DDI study and the Biopharmaceutics BE study are sufficient to support the filing and potential approval of the saxagliptin/dapagliflozin FDC NDA (See Section 7.1)?

FDA Response:

You proposed to study the bioequivalence of the (b) (4)

(b) (4) strength

(5 mg saxagliptin/10 mg dapagliflozin fixed dose combination tablet versus 5 mg saxagliptin individually coadministered with 10 mg dapagliflozin under fasting condition) as well as the high-fat-meal-effect studies for (b) (4)

(b) (4) 5 mg saxagliptin/10 mg dapagliflozin fixed dose combination tablet. Your proposed program appears sufficient to support the Biopharmaceutics aspect of a New Drug Application (NDA) for (b) (4)

(b) (4) 5 mg saxagliptin/10 mg dapagliflozin) fixed dose combination tablets. See the "Biowaiver" response below for the remaining strengths of the saxagliptin/dapagliflozin fixed dose combination tablets.

Since the efficacy and safety studies supporting the use of the saxagliptin/dapagliflozin fixed dose combination tablets are being conducted as add-on to other existing therapy such as metformin, in your NDA submission you need to address the potential mutual interactions among the existing therapy, saxagliptin, and dapagliflozin.

Sponsor Response to Preliminary Comments:

On June 20, 2014, the sponsor sent the following response by email, regarding the statement, "Since the efficacy and safety studies supporting the use of the saxagliptin/dapagliflozin fixed dose combination tablets are being conducted as add-on to other existing therapy such as metformin, in your NDA submission you need to address the potential mutual interactions among the existing therapy, saxagliptin, and dapagliflozin":

In the Summary of Clinical Pharmacology to be included in the saxagliptin/dapagliflozin FDC NDA submission, AZ will plan to provide a summary of results from in vitro and in vivo studies conducted with each component of the saxagliptin/dapagliflozin FDC to assess the potential for drug-drug interactions with other anti-diabetics. Does FDA agree that this will satisfy their request for an assessment of potential mutual interactions amongst the existing therapy, saxagliptin and dapagliflozin?

FDA's Response Dated June 20, 2014:

The sponsor needs to consider results from the available drug-drug interaction studies and provide justification supporting no significant mutual interactions amongst the existing therapy, saxagliptin and dapagliflozin. The proposed data is sufficient to address this question.

Meeting Discussion: *There was no discussion on this question at the meeting.*

Biowaiver:

Based on the demonstration of BE of the [REDACTED] (b) (4) strength (5 mg saxagliptin/10 mg dapagliflozin fixed dose combination tablet versus 5 mg saxagliptin individually coadministered with 10 mg dapagliflozin under fasting condition),

[REDACTED] (b) (4)

When requesting for biowaivers, you need to provide formulation composition for all the strengths of your FDC products along with dissolution profiles comparison and f2-values using 12 units of each dosage strength and using the final dissolution method. [REDACTED] (b) (4)

Of note, biowaiver will be granted only during NDA review.

We assume that at this point, your dissolution method is under development. We request that you develop a dissolution method for both analytes of your drug product, and submit the following dissolution information:

1. **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
 - a. Solubility data for the drug substance covering the pH range;
 - b. 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 $\frac{(b)}{(4)}$ % 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;
 - c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. 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*);
 - d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (*i.e.*, $\pm \frac{(b)}{(4)}$ % change to the specification-ranges of these variables);
 - e. Supportive validation data for the dissolution method (*i.e.*, method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:
 - a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (*i.e.*, specification-sampling time point and specification value).
 - b. The *in vitro* dissolution profile should encompass the timeframe over which at least $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - c. For immediate release product the selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs.

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.

Meeting Discussion: There was no discussion on this question at the meeting.

Clinical Program Questions

Question 3

There are three Phase 3 clinical studies (CV181169, CV181168, and MB102129) being conducted under the saxagliptin or dapagliflozin INDs to evaluate the safety and efficacy of the saxagliptin and dapagliflozin combination in subjects with T2DM. Based on Agency feedback relative to the review of the study synopsis (Agency correspondence received on 10-Apr-2012), Study CV181169 (24 weeks, N = 534), which utilizes a dual add-on to metformin XR strategy with saxagliptin + dapagliflozin, is intended to provide the substantial evidence to support the review and approval of the NDA for the saxagliptin and dapagliflozin FDC product. The other two studies (24 weeks plus long-term (LT) extension to 52 weeks) are being conducted as sequential add-on studies for both saxagliptin (in dapagliflozin/metformin immediate release (IR) failures [CV181168, planned N = 280]) and for dapagliflozin (in saxagliptin/metformin IR/extended release (XR) failures [MB102129, planned N = 280]). The sequential add-on studies are intended to support the safety evaluation of the saxagliptin/dapagliflozin FDC product

[REDACTED] (b) (4)

Does the Agency agree [REDACTED] (b) (4)
[REDACTED] ?

FDA Response:

We do not agree [REDACTED] (b) (4)
[REDACTED]
[REDACTED] **Efficacy data from all studies submitted as part of the initial NDA submission should be included.** [REDACTED] (b) (4)

[REDACTED] **Based on your**

subsequent questions, you appear to be aware that this may be an issue. Our concerns with regard to this will be addressed under the appropriate questions.

Meeting Discussion:

AstraZeneca requested clarification on the reasoning for requesting 52 week exposures now compared to the advice received in 2012 which stated 24 weeks exposure would be adequate. The FDA stated that our previous experience with fixed dose combinations have typically been in combination with metformin. Since combination with metformin is usually studied extensively in the development program of the individual component, there is generally sufficient safety information to evaluate. With the proposed combination product, the experience is limited making safety of the combination a concern. (b) (4)

The FDA stated that further review of this study with internal discussion would be needed to assess whether this study provides sufficient data to satisfy the safety concerns and to allow for evaluation of efficacy only to support the fixed dose combination.

Post-meeting Comments:

We have reviewed the clinical study synopsis provided for study D1690C00010. We note that with regard to safety, the synopsis focuses primarily on adverse events of concern with dapagliflozin. We were unable to identify any discussion on the impact of combining these two drug products on the adverse events of concern for DPP-4 inhibitors (i.e. sitagliptin). Without this information, we cannot agree to rely on this study to support the safety profile of combining an SGLT2 inhibitor with a DPP-4 inhibitor (i.e. the proposed combination of saxagliptin and dapagliflozin).

Question 4

Does the Agency agree (b) (4)

?

FDA Response:

See our response above. (b) (4)

Meeting Discussion: *There was no discussion on this question at the meeting.*

Question 5

Does the Agency agree (b) (4)

FDA Response:

We will expect there to be data covering 52 weeks of exposure to support the safety of the FDC. As you will likely need to submit data from multiple studies to provide this exposure, we will expect an integrated summary of safety and an integrated summary of efficacy.

Meeting Discussion: There was no discussion on this question at the meeting.

Question 6

Study CV181169 included a 10-mg dose of dapagliflozin. According to the approved US Prescribing Information (USPI) for Farxiga (dapagliflozin) tablets, the recommended starting dose of dapagliflozin is 5-mg once daily (QD), which can be increased to 10-mg QD in patients tolerating dapagliflozin 5-mg QD who require additional glycemic control. It is the Sponsor's position that because CV181169 confirmed the safety of the use of saxagliptin 5-mg and dapagliflozin 10 mg in combination, (b) (4)



Does the Agency agree



FDA Response:



Meeting Discussion:

(b) (4)

Question 7

Does the Agency agree that summaries in Module 2 (to include Biopharmaceutics, Clinical Pharmacology, Efficacy, Safety, and a Clinical Overview), as well as a (b) (4) report in Module 5.3.5.3 will be sufficient for filing of the saxagliptin/dapagliflozin FDC NDA?

FDA Response:

See our responses above. We are uncertain whether your proposal for the contents of the initial NDA submission are adequate to demonstrate safety and efficacy. A decision on whether the application is sufficient for filing would be made at the time of filing and would involve many review disciplines.

Meeting Discussion: *There was no discussion on this question at the meeting.*

4-Month Safety Update (4MSU) Questions

Question 8

In the 4MSU, (b) (4) safety data (b) (4) will be included. (b) (4)

The Sponsor proposes to submit completed clinical study reports and data (b) (4)

Does the Agency agree with the proposal to provide (b) (4) the safety data (b) (4) in the 4MSU, along with updated Modules 2.7.4 and 2.5?

FDA Response:

We do not agree. See our responses above. We expect that the information from study CV181168 and/or study MB102129 will be submitted in the initial NDA and integrated with the data from CV181169 at the time of NDA submission. This should include the completed data from CV181168 and/or MB10219 which will provide information on exposure to 52 weeks. If both of the studies are not included in the initial NDA submission, the integrated safety data will need to include the available long-term data from the study that was not included. Updating the Summary of Clinical Safety and the Clinical Overview is acceptable. If one of the sequential add-on studies is not included in the initial submission, all of the updated safety information should be included (b) (4)

Meeting Discussion: There was no discussion on this question at the meeting.

Question 9

Does the Agency agree with the proposal (b) (4) ?

FDA Response:

We do not agree. See our responses above. Data from study CV181168 and/or study MB102129 should be submitted with your initial NDA, and should be complete. The 24 week data from CV181169 (b) (4) and safety data for 52 weeks of exposure will need to be submitted. If you do not submit both CV181168 and MB102129 with the initial NDA submission, any additional safety

information submitted in the 4 month safety update should be complete and integrated with the initially submitted data to allow for easy comparison of the initial safety data to the updated safety data (separate and integrated with the initial).

Meeting Discussion: There was no discussion on this question at the meeting.

Pediatric Plan Question

Question 10

The Sponsor has requested a deferral of the requirement to submit pediatric assessment of the saxagliptin/dapagliflozin FDC at the time of the NDA submission. On 16-Apr-2014, an initial pediatric study plan (PSP) was submitted to IND 118840 for the saxagliptin/dapagliflozin FDC product (Sequence No. 0013).

The Sponsor is currently targeting submission of the saxagliptin/dapagliflozin FDC NDA (b) (4) [REDACTED]. Since the initial PSP was submitted on 16-Apr-2014, this allows for at least 210 calendar days (per the PSP guidance) to obtain confirmation of Agency agreement with the initial PSP by the time the NDA is submitted.

In the event the Agency has not confirmed agreement with the initial PSP by the time the NDA is submitted, is there a mechanism for allowing the PSP review to continue in parallel to the submission and review of the saxagliptin/dapagliflozin FDC NDA?

FDA Response:

We plan to provide written comments to you on your iPSP no later than 90 calendar days from the date of receipt of the iPSP, i.e, no later than 90 calendar days from April 16, 2014. You will then have 90 calendar days to submit an Agreed iPSP to the IND. It is incumbent upon you during this 90-day period to make every effort to develop an Agreed iPSP to which FDA will agree. We therefore strongly encourage you to communicate frequently with the review division during this time.

Once you submit an Agreed iPSP, we plan to take no longer than 30 calendar days to provide written comments to you indicating whether we agree with AstraZeneca's Agreed iPSP.

If we have not confirmed agreement with your Agreed iPSP by the time you submit an NDA for the saxagliptin/dapagliflozin FDC proposed product, we will determine whether or not to continue the iPSP review process, depending upon the reasons that agreement was not reached. However, we could decide to refuse to file the NDA, again depending upon the facts and circumstances for non-agreement.

We refer you to the draft guidance entitled "Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans," published July 2013.

Meeting Discussion: There was no discussion on this question at the meeting.

Electronic Submission of the Common Technical Document Question

Question 11

The Sponsor plans to submit this NDA in eCTD format. This application will be submitted following the eCTD structure specified in ICH M2 EWG, *Electronic Common Technical Document Specification v.3.2.2* dated July 2008, and utilizing the recommendations in the FDA Guidance for Industry entitled *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* dated June 2008 and *FDA Implementation of Study Tagging File v.2.6.1* dated June 2008.

Is the proposed format and content of the saxagliptin/dapagliflozin FDC NDA as described above acceptable to the Agency?

FDA Response:

The proposed electronic format is acceptable to the Agency as eCTD is our preferred format for electronic submissions.

You should reference the updated draft FDA Guidance for Industry entitled Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications dated January 2013 for our latest recommendations on eCTD issues.

Meeting Discussion: There was no discussion on this question at the meeting.

Case Report Forms Question

QUESTION 12

Case report forms (CRFs) will be submitted electronically in PDF format as specified in the guidance. CRFs for all deaths, serious adverse events (SAEs), and discontinuations due to AEs occurring within 30 days of the last dose of study medication will be provided for the new clinical studies included with this NDA.

Does the Agency agree with the proposed plans for inclusion of CRFs in the NDA?

FDA Response:

We agree with the proposed CRFs to be included in the NDA. If additional safety concerns arise during the review, we may request additional CRFs.

Meeting Discussion: There was no discussion on this question at the meeting.

Datasets Question**Question 13**

In the initial NDA, clinical study reports and related datasets will be submitted for the Phase 1 bioequivalence study (CV181341), the clinical pharmacology drug-drug interaction study (CV181191), and the dual add-on safety and efficacy study (CV181169). Also, in the initial NDA, collected data and derived analysis data will be provided (b) (4)

In the 4MSU, (b) (4) will be submitted (b) (4)

For (b) (4) the 4MSU, the Sponsor plans (b) (4)

Does the Agency agree with the proposed plans for inclusion of datasets in the NDA and the 4MSU?

FDA Response:

We do not agree with the proposed plan. As discussed above, we will expect data from at least 52 weeks of exposure to the combination of saxagliptin plus dapagliflozin to support safety for the FDC product. We expect that the initial NDA will include data from the completed CV181169, and from CV181168 and/or MB102129. Datasets for all of the studies included in the initial NDA submission should be submitted. For the 4 month safety update, all additional safety data should be presented and integrated, (b) (4)

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified.
- The analysis dataset documentation (Define.pdf) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables.
- The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.

- Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label. In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

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 (CRO) 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 (*Technical Instructions: Submitting Bioresearch Monitoring [BIMO] Clinical Data in eCTD Format*).

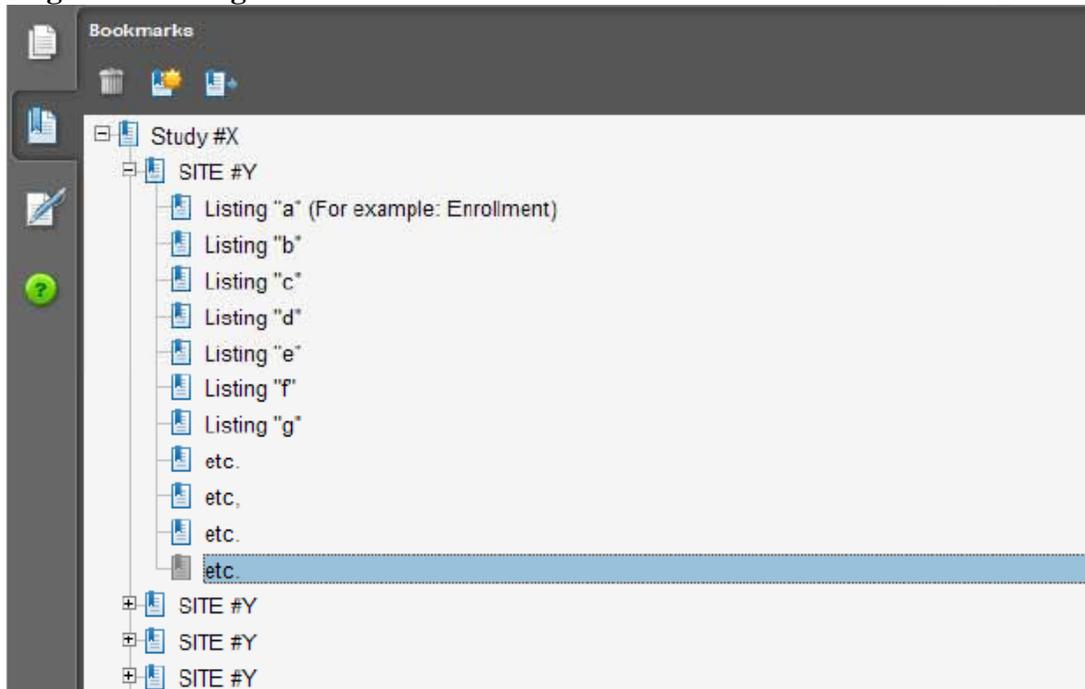
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in the submission, describe the location or provide a link to the requested information).
 1. Please include the following information in a tabular format in the original 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.

Meeting Discussion: There was no discussion on this question at the meeting.

3.0 Additional Information

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

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

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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Issues that require further discussion both internally and with AstraZeneca include:

- duration of exposure for the safety review

(b) (4)

- whether pursuit of an approval
[redacted] would be possible

(b) (4)

5.0 ATTACHMENTS AND HANDOUTS

Sponsor's handouts are attached below

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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
07/23/2014



IND 118840

MEETING PRELIMINARY COMMENTS

AstraZeneca AB
Attention: Chandra Vemavarapu, Ph.D.
Associate Director, Global Regulatory Sciences-CMC
311 Pennington-Rocky Hill Road
Pennington, NJ 08534

Dear Dr. Vemavarapu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Saxagliptin/Dapagliflozin Fixed Dose Combination (FDC) (BMS-986098).

We also refer to your May 9, 2014, correspondence, received May 9, 2014, requesting a meeting to discuss the format and content of the CMC sections of the saxagliptin/dapagliflozin FDC new drug application (NDA), which is currently planned for submission [REDACTED] (b) (4)

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 Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

{See appended electronic signature page}

Danae Christodoulou, Ph.D.
Branch Chief (Acting)
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
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: B
Meeting Category: IND

Meeting Date and Time: July 2, 2014, 10:30am
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1539
Silver Spring, Maryland 20903

Application Number: 118840
Product Name: Saxagliptin/Dapagliflozin Fixed Dose Combination (FDC)
Indication: Type 2 Diabetes
Sponsor/Applicant Name: AstraZeneca AB

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 2, 2014 10:30am, PLACE between AstraZeneca AB and the Division of Metabolic and Endocrine. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

AstraZeneca (AZ, hereafter known as “Sponsor”) with Bristol-Myers Squibb Company (BMS) acting as an Authorized Representative is requesting feedback on the format and content of the CMC sections of saxagliptin/dapagliflozin fixed-dose combination (FDC) NDA, which is currently planned for submission in late 2014. A meeting request, along with the draft questions was submitted to the FDA on May 9, 2014 that was granted as a face-to-face meeting scheduled

for 2nd July, 2014. Final questions along with supporting background information are provided in this briefing document. Reference is made to the Pre-IND interactions with FDA, including the questions from Bristol-Myers Squibb Company submitted on Jul 8, 2013 (Sequence No. 0001), Jul 18, 2013 (Sequence No. 0002), Aug 19, 2013 (Sequence No. 0003) and the respective responses from the agency received on Aug 19, 2013, Sept 16, 2013, and Nov 22, 2013. The advice provided by the Agency in the aforementioned Pre-IND interactions has been incorporated in the pharmaceutical development of saxagliptin/dapagliflozin FDC drug products, as detailed in this briefing document.

2.0 DISCUSSION

2.1. Category/Discipline A

Question 1: Dapagliflozin and saxagliptin both have a high aqueous solubility and saxagliptin/dapagliflozin FDC tablets have an immediate release nature. (b) (4)

(b) (4)
Based on these characteristics and ICH (Q6A and Decision Tree #7) guidance, the Sponsor is proposing to file a disintegration test in lieu of dissolution, (b) (4)

Does the agency concur with the proposal that disintegration testing be included (b) (4) in lieu of dissolution?

FDA Response to Question 1:

Your proposal to include disintegration testing (b) (4) in lieu of dissolution seems reasonable. However, you should submit the following information to support the use of disintegration testing for your drug product:

- Solubility data, including pH-solubility profiles, for saxagliptin and dapagliflozin.
- Data from disintegration experiments to establish a relationship between dissolution and disintegration. Include data that shows that disintegration is more discriminating than dissolution.
- Complete disintegration and dissolution data (i.e. individual, mean, SD, profiles from dissolution testing) for saxagliptin and dapagliflozin.

Question 2: The sponsor proposes (b) (4)

(b) (4)
The proposed strategy is justified (b) (4)

(b) (4)

Does the agency agree with the proposed strategy (b) (4) (for dapagliflozin component only) (b) (4) of FDC drug products?

FDA Response to Question 2:

FDA Response to Question 2: Yes, we agree with the proposed stability testing of the dapagliflozin component.

Question 3: The (b) (4)
sponsor is proposing to employ (b) (4)

FDA Response to Question 3:

Your proposed plan and justification to employ (b) (4) seems reasonable. However, the Agency neither approves (b) (4) nor does it prescribe how to accomplish that goal. The success of process validation is predicated on (i) science and risk-based product and process design, (ii) development of scientifically justified product and process knowledge for a commercial process (iii) leveraging product and process development knowledge for a process validation protocol design, (iv) careful execution of a properly designed process validation protocol, and (v) verification of pre-established protocol outcome via scientifically and statistically justified accept/reject criteria for product quality and batch disposition.

Adequacy of an actual process validation protocol, its execution and study outcome is typically evaluated on an inspection and not through application review. Hence submission of any such information into an application is neither required, nor evaluated as a condition of application approval. Please note that the Process Validation guidance (see below for the reference) states, "The decision to begin commercial distribution should be supported by data from commercial-scale batches."

Nonetheless, in support of your proposal, it is expected that the process validation protocol among other deliverables will include certain objective measures (e.g., acceptance criteria [see 21 CFR 210.3(b)(20)], and appropriate process capability/performance metrics) to demonstrate and assure that the manufacturing process is robust and capable of reliably delivering a product of uniform character and quality across intended product strengths, method of manufacture (e.g., batch or continuous) and production scales (i.e., variable batch size).

For additional information, you are encouraged to refer to “Guidance for Industry, Process Validation: General Principles and Practices” posted at the following link.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

We also encourage you to refer to Agency’s Questions and Answers Resource on Current Good Manufacturing Practices at the following Links on FDA’s website.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm124740.htm>

In particular you may find Agency’s Questions and Answers Resource with regard to Production and Process Controls at the following links useful:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#5>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#15>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#16>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124782.htm#17>

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

/s/

DANAE D CHRISTODOULOU
06/24/2014