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
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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) 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) 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) 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.

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