

**Summary Minutes of the Endocrinologic and Metabolic
Drugs Advisory Committee Meeting
April 14, 2015**

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on April 14, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products (DMEP) and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm426278.htm>

All external requests for the meeting transcript should be submitted to the Center for Drug Evaluation and Research (CDER) Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 14, 2015, at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, AstraZeneca (for the morning session), and Takeda Pharmaceuticals, USA (for the afternoon session). The meeting was called to order by Robert Smith, MD (Chairperson). The conflict of interest statement was read into the record by Philip Bautista, PharmD (Designated Federal Officer). There were approximately 175 people in attendance for the morning session and approximately 125 people in the afternoon session. There were four Open Public Hearing speakers for the morning session and two for the afternoon session.

Issue:

During the morning session, the committee discussed the results of the cardiovascular outcomes trial (CVOT), Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus, for new drug application (NDA) 22350, Onglyza (saxagliptin); and NDA 200678, Kombiglyze XR (saxagliptin and metformin HCl extended-release) tablets manufactured/marketed by AstraZeneca AB.

During the afternoon session, the committee discussed the results of the CVOT, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care, for NDA 22271, Nesina (ALOGLIPTIN); NDA 022426, Oseni (ALOGLIPTIN and PIOGLITAZONE); and NDA 203414, Kazano (ALOGLIPTIN and METFORMIN) tablets marketed by Takeda Pharmaceutical U.S.A., Inc.

Saxagliptin and ALOGLIPTIN are dipeptidyl peptidase-4 (DPP-4) inhibitors, both indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Both CVOTs were submitted in accordance with the 2008 FDA Draft Guidance, "Diabetes Mellitus--Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):

David W. Cooke, MD (Afternoon Session Only); Susan R. Heckbert, MD, PhD; William R. Hiatt, MD, FAHA; James D. Neaton, PhD; Robert J. Smith, MD (Chairperson); Charles A. Stanley, MD (Afternoon Session Only); Peter W. F. Wilson, MD

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present

(Voting): Brendan M. Everett, MD, MPH, FACC, HAHA; Diana Hallare, MPH (Consumer Representative); Ed J. Hendricks, MD

Endocrinologic and Metabolic Drugs Advisory Committee Member (Non-Voting): Mads F.

Rasmussen, MD, PhD (Industry Representative)

Temporary Members (Voting): Bonnie H. Arkus, RN (Acting Consumer

Representative); CAPT Daniel Budnitz, MD, MPH; Kenneth D. Burman, MD; Erica H. Brittain, PhD; Nakela L. Cook, MD, MPH, FACC (Morning Session Only); Gregory McIntyre (Patient Representative); Yves Rosenberg, MD, MPH; Morris Schambelan, MD; Thomas J. Wang, MD; Lamont G. Weide, MD, PhD, FACE

FDA Participants (Non-Voting): Curtis Rosebraugh, MD; Jean-Marc Guettier, MD; Lisa Yanoff, MD (Morning Session Only); Frank Pucino, PharmD, MPH (Morning Session Only); Shanti Gomatam, PhD (Morning Session Only); William Chong, MD (Afternoon Session Only); Valerie S.W. Pratt (Afternoon Session Only), MD; Eugenio Andraca-Carrera, PhD (Afternoon Session Only)

Open Public Hearing Speakers for the Morning Session: Sidney Wolfe, MD (Public Citizen); Robert Ratner, MD (American Diabetes Association); Anne Leddy, MD, FACE (American Association of Clinical Endocrinologists); Kelly Close (diaTribe)

Open Public Hearing Speakers for the Afternoon Session: Anne Leddy, MD, FACE (American Association of Clinical Endocrinologists); Manu Venkat (Close Concerns)

The morning session agenda proceeded as follows:

Call to Order and Introduction of Committee

Robert J. Smith, MD
Chairperson, EMDAC

Conflict of Interest Statement

Philip A. Bautista, PharmD
Designated Federal Officer, EMDAC

FDA Introductory Remarks

Lisa Yanoff, MD
Acting Clinical Team Leader
DMEP, Office of Drug Evaluation (ODE) II
Office of New Drugs (OND), CDER, FDA

SPONSOR PRESENTATIONS

AstraZeneca AB

Introduction

Howard Hutchinson, MD
Vice President, Global Medicines Development
AstraZeneca

SAVOR TIMI-53 Study Design & Results

Benjamin M. Scirica, MD, MPH
TIMI Study Group
Brigham and Women's Hospital
Harvard Medical School

Perspectives on the Treatment of Diabetes
and the SAVOR Data

Jay S. Skyler, MD, MACP
Division of Endocrinology, Diabetes, and Metabolism
and Diabetes Research Institute
University of Miami Miller School of Medicine

Conclusion

Howard Hutchinson, MD

Clarifying Questions

FDA PRESENTATIONS

Saxagliptin Assessment of Vascular
Outcomes Recorded in Patients with
Diabetes Mellitus (SAVOR)

Frank Pucino, PharmD, MPH
Clinical Reviewer
DMEP, ODE II, OND, CDER, FDA

Statistical Assessment of CV Safety

Shanti Gomadam, PhD
Statistician
Division of Biometrics (DB) VII
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER FDA

Assessment of Safety and Summary

Frank Pucino, PharmD, MPH

Clarifying Questions

BREAK

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURN

The afternoon session agenda proceeded as follows:

Call to Order and Introduction of Committee	Robert J. Smith, MD Chairperson, EMDAC
Conflict of Interest Statement	Philip A. Bautista, PharmD Designated Federal Officer, EMDAC
FDA Introductory Remarks	William Chong, MD Acting Clinical Team Leader DMEP, ODE II, OND, CDER, FDA
SPONSOR PRESENTATIONS	Takeda Pharmaceutical U.S.A., Inc.
Introduction	Stuart Kupfer, MD Vice President, Clinical Science CVM Takeda Development Center Americas, Inc.
EXAMINE Study Results	William B. White, MD Chair, EXAMINE Steering Committee Professor of Medicine Calhoun Cardiology Center University of Connecticut School of Medicine
Clinical Perspective	Marc Pfeffer, MD, PhD Dzau Professor of Medicine Harvard Medical School Cardiovascular Division Brigham & Women's Hospital
Overall Safety and Conclusions	Stuart Kupfer, MD
Clarifying Questions	
FDA PRESENTATIONS	
Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE)	Valerie S.W. Pratt, MD Medical Officer DMEP, ODE II, OND, CDER, FDA
Statistical Methods and Results	Eugenio Andraca-Carrera, PhD Statistician DB VII, OB, OTS, CDER, FDA
Assessment of Safety and Summary	Valerie S.W. Pratt, MD

Clarifying Questions

BREAK

Open Public Hearing

Questions to the Committee/Committee Discussion

ADJOURN

Questions to the Committee (Morning Session):

1. **DISCUSSION:** Discuss the overall findings in SAVOR, and in your discussion, specifically address the following:

- a. Comment on your level of concern with regard to the all-cause mortality findings in SAVOR.

***Committee Discussion:** The majority of the committee agreed that there was a moderate concern for the all-cause mortality findings in SAVOR. The committee noted that the statistically significant findings were based on sensitivity analyses that censored deaths near treatment exposure and were uncertain about the strength and validity of these sensitivity analyses. Nevertheless, the committee agreed that all-cause mortality was a fundamentally strong endpoint, and that an effect on all-cause mortality could not be ruled out. They noted that a major contributing factor to the all-cause mortality findings was unclear, but they agreed that it might be explained in part by the heart failure findings. The committee stated that the uncertainty of these findings could be attributed to the short follow-up time in the study design. Noting that saxagliptin is used to treat a chronic condition, the committee agreed that longer follow-up may help to further evaluate the all-cause mortality findings. Additionally, the committee noted that caution should be used when applying these findings to lower cardiovascular disease risk groups who were not included in the study. Please see the transcript for details of the committee discussion.*

- b. Comment on your level of concern with regard to the heart failure findings in SAVOR.

***Committee Discussion:** The committee agreed that although the study met the requirements of the 2008 FDA Draft Guidance, "Diabetes Mellitus--Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," they were still concerned with regard to the heart failure findings in SAVOR and acknowledged that there is a potential risk. The committee stated their belief that saxagliptin is safe to use in the general population. They noted, however, that until this risk is further explored caution and additional monitoring is necessary in patients at higher cardiovascular risk, especially those with an eGFR ≤ 60 mL/min and with a prior history of heart failure. The committee agreed that further studies are needed to explain the mechanism by which saxagliptin and other DPP-4 inhibitors might increase the risk for heart failure and to help further identify which patient populations are most at risk. Until the risks and mechanism are further defined, the committee agreed that these heart failure findings should be communicated to health care professionals and their patients. Please see the transcript for details of the committee discussion.*

- c. In contrast to glycemic efficacy trials, SAVOR was enriched with a population of patients with type 2 diabetes who also had baseline renal impairment. Please comment on the renal safety findings in SAVOR.

Committee Discussion: *The committee agreed that there was a low level of concern for the renal safety findings in SAVOR. The committee made note of the contrasting potentially harmful and protective findings with regards to observed decreases in eGFR and reduced albuminuria in some patients. However, the committee agreed that the SAVOR trial was not designed to answer questions regarding renal safety given the relatively short treatment exposure and follow-up times in the study. The committee agreed that the potential renal safety signal in the study should be further explored in observational studies. Please see the transcript for details of the committee discussion.*

- d. Comment on any additional safety concerns which were not discussed above (e.g., hypersensitivity, pancreatitis, or other).

Committee Discussion: *The committee agreed that there was a numerical excess of definite acute pancreatitis in the saxagliptin group vs. placebo. Given the limited data available, the committee could not conclude on whether this was a significant safety risk. However, the committee agreed that this potential risk should continue to be monitored. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Based on information presented today and in the background materials, do the results of SAVOR demonstrate that the use of saxagliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile?

Vote Results: YES = 13 NO = 1 ABSTAIN = 1

- a. Explain your rationale and recommend additional studies if you believe these are needed.

Committee Discussion: *The majority of the committee (13 members) agreed that the study met the requirements of the 2008 FDA Draft Guidance, "Diabetes Mellitus--Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," and that the results of SAVOR demonstrated that the use of saxagliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile based on the presentations and background materials provided. The member voting no stated that the overall cardiovascular risk-benefit profile was unfavorable because of the potential heart failure finding and cited the unknown mechanism of heart failure. One member of the committee abstained from the vote due to needing more information. The majority of the committee reiterated their concern for the heart failure hospitalization findings and recommended additional observational studies to further explore this safety signal, especially in patients with higher cardiovascular risk (such as those with previous heart failure and/or impaired renal function). The committee stated that it would be unreasonable to expect that saxagliptin would alter survival in the patients who were at a more advanced stage of disease and emphasized that interventions need to occur early on in order to potentially increase survival. Moving forward, the committee agreed that caution should be taken in patients with a previous history of heart failure and/or*

impaired renal function. Please see the transcript for details of the committee discussion.

3. **VOTE:** Which action do you recommend FDA take regarding the totality of the safety information (Cardiovascular and other) obtained in SAVOR? After the voting is completed, please explain your answer and specify the safety issue(s) of concern, if applicable. Also recommend additional studies if any are needed.
- A. No change to labeling (i.e., no new safety information needs to be added to the label)
 - B. Change labeling to add new safety information
 - C. Change labeling to add new safety information and restrict distribution
 - D. Withdraw saxagliptin from the market

Vote Results: A = 0 B = 14 C = 0 D = 1

Committee Discussion: *The majority of the committee (14 members) voted that changes should be made to the saxagliptin labeling to add new safety information, including potential increased risk of heart failure, all-cause mortality, decreased renal function, and acute pancreatitis based on the safety findings from the SAVOR trial. The committee further specified that labeling should communicate the potential increased risk for heart failure in patients with a previous history of heart failure and decreased renal function. The majority of the committee agreed that restriction of distribution is not needed. One member of the committee voted to withdraw saxagliptin from the market because SAVOR did not demonstrate a cardiovascular benefit. The committee did not recommend any additional studies. Please see the transcript for details of the committee discussion.*

Questions to the Committee (Afternoon Session):

1. **DISCUSSION:** Discuss the overall findings in EXAMINE, and in your discussion, specifically address the following:
- a. Nominally significant interactions in the risk of major adverse cardiac events (MACE) were identified in some subgroup analyses across distinct geographic regions and baseline disease/demographic characteristics. Please comment on the relevance of these findings in informing CV-risk associated with the use of alogliptin.

Committee Discussion: *The committee agreed that there was limited concern regarding the nominally statistically significant interactions in the risk of MACE identified in some subgroup analyses across distinct geographic regions and baseline disease/demographic characteristics. The committee agreed that more emphasis should be placed on the primary outcomes of the study in the combined data. The committee stated that further subgroup analyses combining U.S., Canada, and Western European data might be warranted. Please see the transcript for details of the committee discussion.*

- b. Please comment on the heart failure findings in EXAMINE. In your response comment on how specifics of the EXAMINE trial design (e.g., specific enrichment strategy) factor into your opinion, if at all.

Committee Discussion: *The committee agreed that there was a minor concern for heart failure risk given the inconclusive findings of EXAMINE. However, the committee stated that a causal link between alogliptin and heart failure was difficult to establish due to the study population's pre-existing increased risk for cardiovascular death and the timing of the study outcomes (i.e., hospitalization for heart failure). Given this ambiguity, the committee recommended monitoring the results from other DPP-4 inhibitor CVOTs to further assess the potential for a drug class effect. Please see the transcript for details of the committee discussion.*

- c. In contrast to glycemic efficacy trials, EXAMINE was enriched with a population of patients with type 2 diabetes who also had baseline renal impairment. Please comment on the renal safety findings in EXAMINE.

Committee Discussion: *The committee agreed that the study design did not allow enough alogliptin exposure and follow-up to adequately assess the renal safety of alogliptin in this study population. The committee agreed that monitoring of all DPP-4 inhibitors for a potential renal safety signal is warranted. Please see the transcript for details of the committee discussion.*

- d. Comment on any additional safety concerns which are not discussed above (e.g., hypersensitivity reactions, pancreatitis, or other).

Committee Discussion: *The committee agreed that the potential for hepatotoxicity, severe cutaneous reactions, and hypersensitivity reactions with alogliptin are rare, but should still be monitored. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Based on information presented today and in the background materials, do the results of EXAMINE demonstrate that the use of alogliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile?

Vote Results: YES = 16 NO = 0 ABSTAIN = 0

- a. Explain your answers and recommend additional studies if you believe these are needed.

Committee Discussion: *The committee unanimously agreed that the study met the requirements of the 2008 FDA Draft Guidance, "Diabetes Mellitus--Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," and based on the presentations and background materials provided by FDA and Takeda Pharmaceuticals, USA, the results of EXAMINE demonstrate that the use of alogliptin in patients with type 2 diabetes has an acceptable cardiovascular risk profile. The committee reemphasized that the study had unanticipated limitations including the inclusion criteria, the lack of patient recruitment in the U.S., and the short follow-up time. There was comment that the design of EXAMINE may not have been the best study design to answer the safety questions of interest. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Which action do you recommend FDA take regarding the totality of the safety information (Cardiovascular and other) obtained in EXAMINE? After the voting is completed, please explain your answer and specify the safety issue(s) of concern, if applicable. Also recommend additional studies if any are needed.
- A. No change to labeling (i.e., no new safety information needs to be added to the label)
 - B. Change labeling to add new safety information
 - C. Change labeling to add new safety information and restrict distribution
 - D. Withdraw alogliptin from the market

Vote Results: A = 3 B = 13 C = 0 D = 0

Committee Discussion: *The majority of the committee (13 members) voted that changes should be made to alogliptin's labeling to include information on the results EXAMINE and to include new safety information regarding the risk for heart failure, and renal impairment. One committee member commented that the findings for MACE in the U.S. population and the findings from the analysis of liver safety could also be considered for labeling. Three members of the committee voted that no changes should be made to alogliptin's labeling given the totality of safety data (Cardiovascular and other) obtained in EXAMINE. The committee did not recommend any additional studies. Please see the transcript for details of the committee discussion.*

The morning session was adjourned at approximately 12:05 p.m., and the afternoon session was adjourned at approximately 5:05 p.m.