

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: No Format Deficiencies

Product Title¹	FARXIGA (dapagliflozin) tablets, for oral use
Applicant	Bristol Myers Squibb
Application/Supplement Number	NDA 202293
Type of Application	Resubmission Class 2
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Office/Division	ODE II, DMEP
Division Project Manager	Abolade Adeolu
Date FDA Received Application	July 11, 2013
Goal Date	January 11, 2014
Date PI Received by SEALD	January 8, 2014
SEALD Review Date	January 9, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, agreed-upon prescribing information (PI) for important format elements reveals **no outstanding labeling format issues** and the SEALD Director has **no objection** to the approval of this PI at this time.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

Selected Requirements of Prescribing Information

- N/A** 12. All text in the BW must be **bolded**.
Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
Comment:
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
Comment:
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.
Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JEANNE M DELASKO
01/09/2014

ERIC R BRODSKY
01/09/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 20, 2013

To: Abolade Adeolu, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 202293
OPDP labeling comments for Farxiga (dapagliflozin) tablet, film-coated

OPDP has reviewed the proposed draft prescribing information (PI) for Farxiga (dapagliflozin) tablet, film-coated (Farxiga) submitted for consult on August 5, 2013.

OPDP's comments regarding the draft medication guide were previously provided under separate cover on December 18, 2013.

OPDP's comments on the proposed draft PI are based on the version located in the eRoom entitled, "202293dapag-markup 12-19-13" (last modified December 20, 2013) and are provided on the marked version provided directly below.

Thank you for the opportunity to comment on the proposed draft PI.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
12/20/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 18, 2013

To: Jean-Marc Guettier, MD
Acting Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Twanda Scales RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): FARXIGA (dapafliglozin)

Dosage Form and Route: tablets

Application Type/Number: NDA 202293

Applicant: Bristol-Myers Squibb

1 INTRODUCTION

On December 28, 2010, Bristol-Myers Squibb submitted for the Agency's review an Original New Drug Application for dapagliflozin tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. On January 17, 2012, the Agency issued a Complete Response (CR) letter. Bristol-Myers Squibb resubmitted the application on July 13, 2013.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) on August 5, 2013, and August 5, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FARXIGA (dapagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft FARXIGA (dapagliflozin) MG received on July 13, 2013, and received by DMPP on December 16, 2013.
- Draft FARXIGA (dapagliflozin) MG received on July 13, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 18, 2013.
- Draft FARXIGA (dapagliflozin) Prescribing Information (PI) received on July 13, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 16, 2013.
- Draft FARXIGA (dapagliflozin) Prescribing Information (PI) received on July 13, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 18, 2013.
- Approved INVOKANA (canagliflozin) comparator labeling dated March 29, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
12/18/2013

KENDRA Y JONES
12/18/2013

MELISSA I HULETT
12/18/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: November 18, 2013

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Farxiga (Dapagliflozin), 5 mg and 10 mg

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol-Myers Squibb

OSE RCM #: 2013-1640

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and prescribing information for Farxiga (Dapagliflozin) NDA 202293 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant, Bristol-Myers Squibb submitted a request for review of the proposed label and labeling for Farxiga (Dapagliflozin), on October 16, 2013 as part of NDA 202293.

1.2 PRODUCT INFORMATION

- Active Ingredient: Dapagliflozin
- Indication of Use: Indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 5 mg and 10 mg
- Dose and Frequency: One tablet (5 mg or 10 mg) daily, regardless of meals
- How Supplied: Bottles of 30, 90, 500; Hospital Unit dose, Cartons of 100 tablets; Professional Sample, 7 tablets
- Storage: Store at 20°C to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].
- Container and Closure System: 95-cc high density polyethylene (HDPE) bottle (b) (4) and 200-cc (b) (4) HDPE bottle (b) (4). The additional commercial (b) (4) presentation is (b) (4) blister.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 16, 2013 and November 4, 2013 (Appendix A)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton Labeling submitted October 16, 2013 (Appendix B)
- Professional Sample Carton Labeling submitted October 16, 2013 (Appendix C)
- Hospital Unit-Dose Blister labels submitted October 16, 2013 (Appendix D)
- Unit-Dose Carton Labeling submitted October 16, 2013 (Appendix E)
- Prescribing Information submitted November 14, 2013 (not included)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the carton and container label for this NDA (OSE #2011-24, dated December 9, 2011) and we looked at the review and most of our previous recommendations were implemented.

3 CONCLUSIONS

Although majority of our recommendations were implemented, we conclude that the proposed label, labeling and design can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information. Thus, Section 3.1 Comments to the Applicant contains our recommendations for the carton and container labels.

4 RECOMMENDATIONS

4.1 COMMENTS TO THE DIVISION

- A. The Dosage and Administration section contains dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:

- a. Revise all instances of the symbol '<' or '>' in the text. The 'greater than' and 'less than' symbols are dangerous abbreviations that could be interpreted opposite of its intended meaning.

4.2 COMMENTS TO THE APPLICANT

- A. Commercial Size Product Labels and Labeling (All Strengths)
1. Revise the presentation of the proprietary name from all lowercase (e.g. farxiga) to title case (e.g. Farxiga) to increase readability.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

2. Revise the font color of the proprietary name (red color) or revise the color scheme of the 10 mg strength (b) (4) so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.

(b) (4)
which may lead to wrong strength selection errors.

B. Hospital Unit Dose Blisters

Revise the presentation of the strength statement to the same color scheme as in the container labels to better differentiate the strengths (i.e. 5 mg (b) (4) and 10 mg (b) (4)), if feasible. Additionally, see comment A2 regarding 10 mg color scheme.

C. Professional Samples

1. Container Label

- i. Revise the presentation of the strength statement to the same color scheme as in the container labels to better differentiate the strengths (i.e. 5 mg (b) (4) and 10 mg (b) (4)), if feasible. Additionally, see comment A2 regarding 10 mg color scheme.
- ii. Delete (b) (4) beside the number of tablets to only read “7 Tablets.”

2. Carton Labeling

- i. Remove (b) (4)
- ii. Delete (b) (4) beside the number of tablets to only read “7 Tablets”
- iii. Revise the strength presentation from XX mg to read “XX mg per tablet” located inside the boxing.
- iv. Increase the prominence of the statement “Physician Sample- NOT FOR SALE.” As currently presented, this statement is embedded in the blue or red highlight, making it difficult to read.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

9 Page(s) of Draft Labeling 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/

REASOL AGUSTIN
11/18/2013

YELENA L MASLOV
11/19/2013

Clinical Consultation Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 10 November 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology(OPE), Office of Surveillance and Epidemiology (OSE)

TO: Jean Marc Guettier, M.D., Acting Director, Division of Metabolism and Endocrinology Products (DMEP), Office of New Drugs II (OND II), Eric Colman, M.D., Deputy Director, DMEP
Amy Egan, M.D. Deputy Director for Safety, DMEP
Karen Mahoney, M.D., Clinical Team Leader, DMEP
Frank Pucino, Ph.D., Clinical Reviewer, DMEP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of dapagliflozin for treating diabetes mellitus, NDA 202293 submitted 27 December 2010 by Bristol-Myers Squibb; Complete Response 17 January 2012, and resubmission 11 July 2013

Documents reviewed:

- 1) Consultation request dated 22 August 2013 entered into DARRTS as FRM CONSULT-06 (OSE Consult) by Abolade Adeolu of DMEP, with desired completion date 22 September, forwarded by Marguerita Tossa of OSE, assigned consultation tracking number #2013-1922
 - 2) Reports from sponsors' Bristol-Myers Squibb and Astra Zeneca: Hepatic Adjudication Report dated 19 June 2013 (367 pages), updating of initial report 14 April 2011, with corrections on 10 May (3 pages) and addendum 25 October 2011 (114 pages), plus Response to Complete Response Letter dated 24 June 2013 (18 pages), and draft commentary on Hepatic Safety of dapgliflozin by Dr. Pucino ,forwarded on 17 October 2013
 - 3) Update (30-month) on dapagliflozin 10 June 2013, delivered by Dr. Pucino 23 October 2013
 - 4) Memo by Dr. Mary Parks, 22 December 2011, explaining reasons for Complete Reseponse dated 27 January 2012
 - 5) Sponsors' Hepatic Adjudication Report, 13 June 2013 (367 pages)
 - 6) Pharmacovigilance review 3 October 2013, Dr. Christine Chameralain, DPV1/OHOP, on post-marketing findings on Forxiga (dapagliflozin) approved in Europe, Australia, Mexico, and on cangliflozin, regarding breast and bladder cancer
 - 7) Oncology consultation, 21 October 2013, Dr. Genevieve Schecter, DOP1/OPE/OSE, concerning breast and bladder cancer information
 - 8) Sponsors' 4 November "backgrounder" for 12 December 2013 Advisory Committee meeting
 - 9) Selected pertinent medical literature from NIH PubMed program
-

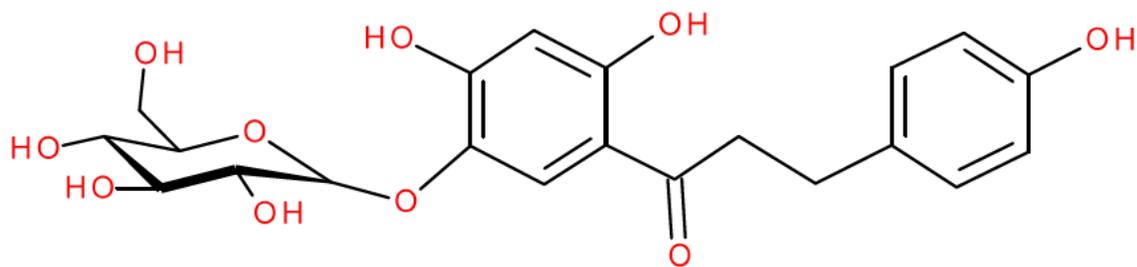
The request from the review division asked for 30-day response to questions, anticipating an advisory committee review in December (within six months of the resubmission 11 July 2013). The original NDA 202293 for dapagliflozin was submitted 27 December 2010, after more than 7 years of development under IND 068052 submitted 21 November 2003. After careful review by Dr. Somya Dunn, clinical reviewer, and concurring review by Dr. Mary Parks, then-Director of DMEP, it was not approved and a Complete Response was sent 17 Jan 2012, citing problems with insufficient assurance of safety from bladder and breast cancer, a single case of probable Hy's Law liver injury, and suggestive but not convincing compensating cardiovascular benefit from a meta-analysis discordant with repeat DMEP analyses. Recommendations were sent to the sponsor requesting updated information on the bladder and breast cancer incidence, updated review of hepatic safety, and updated meta-analysis of major cardiovascular events. The sponsor complied with these recommendations and submitted a resubmission on 11 July 2013, after some months of discussions and negotiation. Dr. William Chong replaced Dr. Dunn as clinical reviewer temporarily from 7 February to 3 September 2013, when Dr. Frank Pucino succeeded him. Dr. Chong does not appear to have made any DARRTS entries during the temporary appointment.

The request from Dr. Pucino asks for review from the "DILI team" (me) on cases that meet the definition of Hy's Law and other serious hepatic adverse events in the pooled phase 2b and 3 clinical trials, the incidence of transaminase elevations at 3, 5, 10, and 20 times the laboratory upper reference limit, the likelihood of dapagliflozin contributing to drug-induced liver injury (DILI), and any additional recommendations for hepatic safety. Because of the sponsor's posting a Dispute Resolution, a second Advisory Committee (AC) is to be convened 12 December 2013..

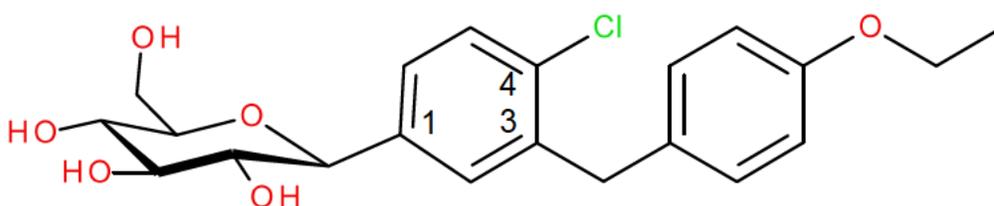
Dapagliflozin is a selective inhibitor of the proximal tubular sodium-dependent glucose co-transporter-2 receptors (SGLT-2s). The drug is a phlorizin derivative, with a glucose moiety at one end and an aromatic-aliphatic chain. Phlorizin is found naturally in the bark of fruit trees such as apple, pear, and cherry. Derivatives of phlorizin, with modifications of the aromatic-aliphatic chain that confer better and more selective properties, as dapagliflozin developed by the sponsor of this NDA, while canagliflozin and empagliflozin were developed by others. Another analog, tofogliflozin, is in phase 3 development by Chugai (b) (4)

The story of how the -gliflozins were rapidly developed recently started with recognition (von Mering, 1886) that phlorizin (then phlorhizin) caused glucosuria, and it was dubbed "phlorhizin diabetes" (Ringer, 1910). It was shown by Mayrs (1923) that proximal renal tubular epithelium reabsorbed the glucose filtered by glomeruli, and that was inhibited by phlorhizin. Rosetti and colleagues in 1987 showed that inducing glucosuria by phlorizin reduced plasma glucose levels, restoring sensitivity to insulin in diabetic rats. The race then began to find analogues of phlorizin more specific to renal tubules, less toxic, and patentable. The first of these seems to have been dapagliflozin, patented by Bristol-Myers Squibb in 2002, and its IND was submitted for clinical trials to begin in 2003 (Meng et al., 2008). The vast potential use for a new approach to type 2 diabetes, expected to rise to more than 300 million people world wide, was attractive to many sponsors of new drugs.

The very close resemblance of natural phlorizin and the new synthetic derivatives is evident from their molecular structures, all with a D-glucose moiety attached to a slightly different side chain:

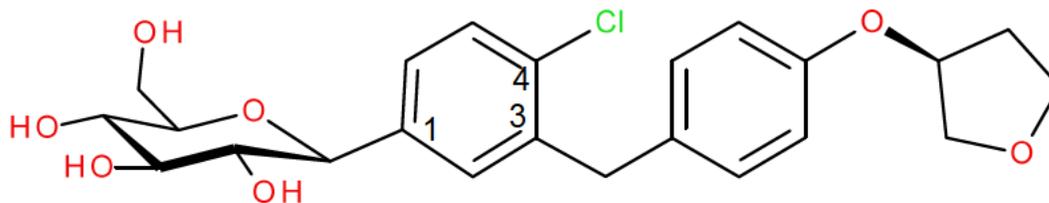


phlorizin (phlorhizin)



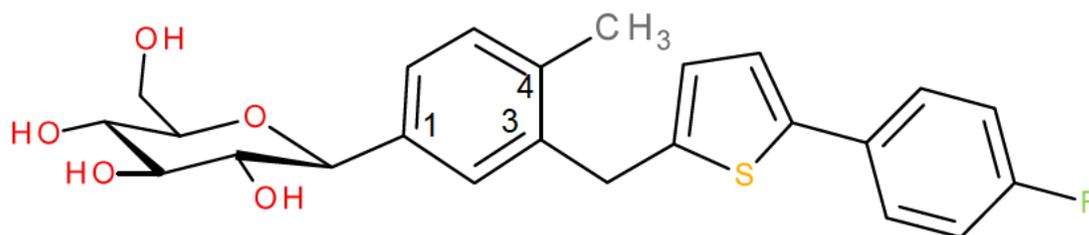
dapagliflozin

IND 21 Nov2003; NDA 27 Dec 2010;
CR 17 Jan 2012; resub 11 Jul 2013
Bristol Myers-Squibb, AstraZeneca



empagliflozin

IND [REDACTED] ^{(b) (4)} NDA 5 Mar 2013
Boehringer Ingelheim, Lilly



canagliflozin

IND 24 Jan 2011; NDA 31 May 2011
AP 29 Mar 2013; Janssen INVOKANA

Canagliflozin, although the most recently developed member of the class, was quickly approved in March 2013, with no labeled warnings about liver toxicity. (b) (4)

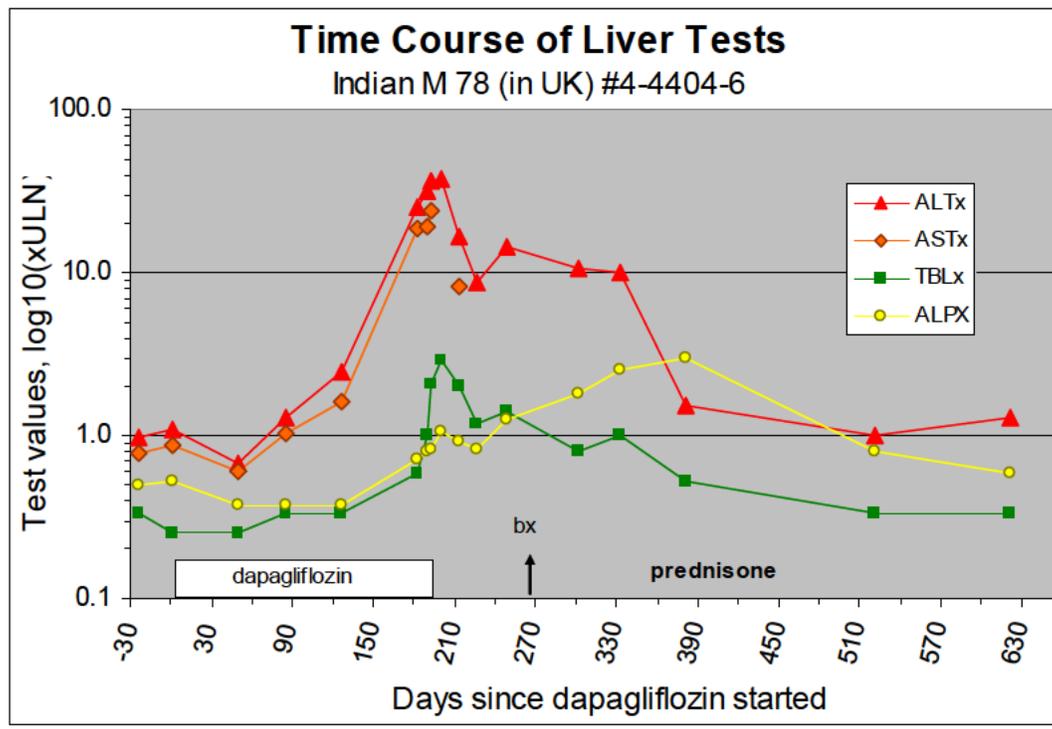
The question then is if and why dapagliflozin might pose a greater risk of potentially serious liver injury in some patients. Having shown at least one case adjudicated as probably dapagliflozin-induced, although possibly it was autoimmune hepatitis..

It should be emphasized at the outset that Hy's Law is NOT defined by elevated serum ALT activity $>3xULN$ and total bilirubin (TBL) concentration $>2xULN$. Those rather conservatively low cut-points serve only identify patients of special interest for careful consideration of what may have caused the abnormalities. The key element of the Zimmerman observation and first stated, is that the hepatocellular injury be *drug-induced*, that is, actually caused by the person's response to the drug, and not by disease, some other compound, or some other cause. The cause of liver injury is often difficult to determine, and seldom can be done just from information that is collected routinely in clinical trials and recorded in study case records. It is therefore of no use to have the sponsor simply summarize the case reports when asked to submit a clinical narrative that describes the evolution of the case, what was done to investigate it, and the reasoning that went into making a best estimate of the most likely cause. It is seldom possible to be certain of the cause, for drugs may cause a great variety of different reactions that can mimic any known disease cause of an acute hepatitis, and even liver biopsy is not diagnostic. The best that often can be said, after a reasonable attempt to make a clinical diagnosis, is that the other possibilities have been pretty well excluded, and the drug may have been the most likely and probable cause ($>51\%$ likely), exceeding all other possible causes combined. This cannot be done by looking just at numbers, and the use of the term "Hy's Law chemistries" should not be used. Preparation of a good narrative should be done by a physician, or someone who is trained and experienced in medical differential diagnosis, so that he or she knows what information should be included.

Another recent realization is that levels of serum elevation of aminotransferase enzyme activity are not a valid measures of injury severity, so that classifications of levels of 3x, 5x, 10x, and 20x the upper limit of a normal reference range are of no value in determining severity. Only the loss of overall liver organ capability to carry out its true functions, such as clearing bilirubin from the plasma, or synthesizing and regulating levels of prothrombin, give a valid indication of functional loss. Only the TBL or INR should be called liver *function tests*; the serum enzyme activities measure only rate of injury and leakage of intracellular enzymes into the plasma. It is a bad practice to allow local laboratories to establish their own ranges of "normal," based on their variable ideas of who is normal or not. The liver is a remarkably adaptive organ; it can regenerate after resection of two-thirds its mass, then regrow rapidly to its original size, and can regain full function. For chemical or drug-induced injury, the liver is now appreciated to show adaptation and replacement of damaged hepatocytes with new and fully functional cells that have acquired tolerance to the injurious agent. Amazing!

In responding to the Complete Response and recommendations from January 2012, additional studies have been done. The website at clinicaltrials.gov lists 59 studies for dapagliflozin, 49 are reported completed and 10 with reports available; 7 listed as recruiting, 1 as not yet recruiting, and 1 each terminated and suspended. We used eDISH in 2011 for a total of 6382 patients: 4519 on dapagliflozin, 1090 on "comparator," 465 on metformin, and 408 on glimepiride.

There was some difficulty in coming to a diagnosis of drug-induced autoimmune hepatitis in the case of the 78-year-old (b) (6) Indian man living in the UK who started taking dapagliflozin 2.5 mg daily (b) (6). He had been diagnosed with heterozygous hemochromatosis. He showed a slight rise in his ALT and AST after 4 months, and marked rise at 6 months, with only slight symptoms of anorexia, dark urine, and upper abdominal discomfort, leading to stopping the drug administration a month later on (b) (6) when his bilirubin had risen to 2.5 mg/dL, about 7 times his baseline values. After stopping the drug, his abnormal test values abated somewhat, but ALT remained quite elevated at 10-14 xULN. Liver biopsy was done on (b) (6), two months after stopping dapagliflozin. Some portal inflammatory infiltrate without frank necrosis was seen, with little fibrosis but some bands of collapsed liver tissue, only mild siderosis. He wrote that the findings “would favour a diagnosis of autoimmune hepatitis.” A four-week course of prednisone from 14 May to 11 June led to a sharp return of the elevated ALT values to almost normal. He was followed closely, and his last test values on 10 February 2010 showed normal bilirubin and alkaline phosphatase, with only minimally elevated ALT of 64 U/L (1.3 xULN). The opinions of three consultants to the sponsor, all well known hepatologists, were mixed concerning the cause of the patient’s abnormal liver tests.



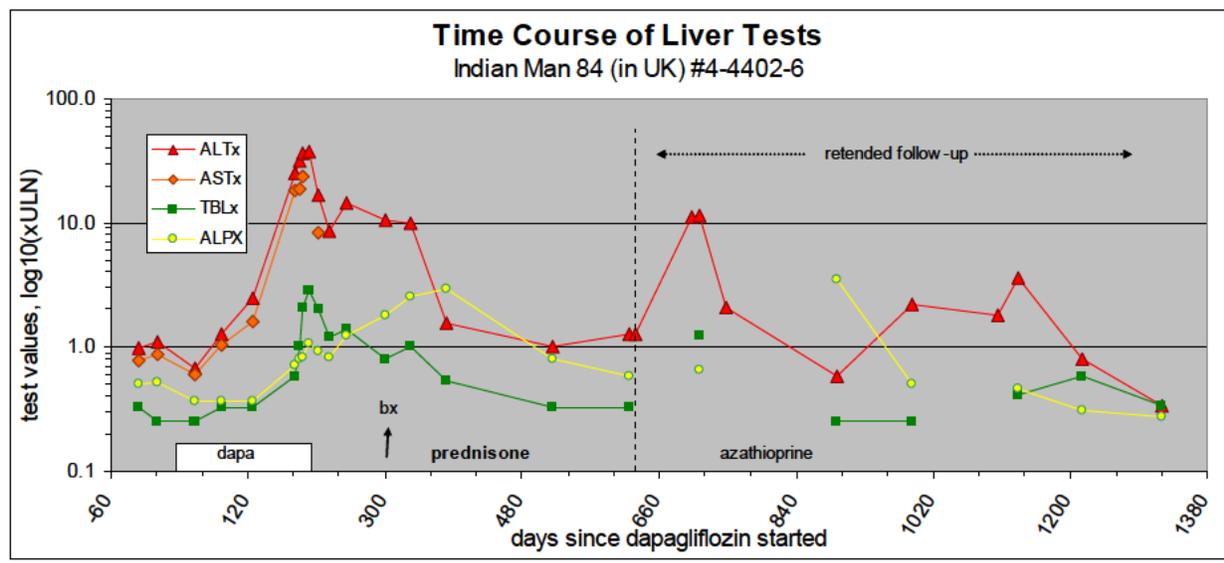
The case was carefully reviewed and adjudicated to be **probably** drug-induced by Dr. Leonard Seeff, who was then consulting for OPE, and was very experienced for five years in determining the most likely causes of cases reported to the DILI Network of U.S. investigators. He finally came down, in this most difficult of differential diagnoses, in a decision written on 3 July 2011.

“Based on these data, despite the histology with features suggestive of autoimmune hepatitis, and even though treatment with corticosteroids was initiated after which liver chemistries improved, a definitive diagnosis of autoimmune hepatitis seems unlikely, since the acute injury

developed for the first time in an older male and the serologic markers of autoimmune hepatitis were negative. Such histology is by no means absolutely indicative of AIH and can be found in other causes of acute liver injury, including drug-induced liver injury. It should be noted that, with discontinuation of dapagliflozin, the serum aminotransferase and bilirubin values began a slow decline but the alkaline phosphatase level continued to increase slightly before falling to a normal level; nevertheless, the pattern of liver dysfunction appeared consistent with that of an acute hepatocellular injury. It is my view, therefore, that the probable diagnosis is mild to moderately severe dapagliflozin-induced liver injury."

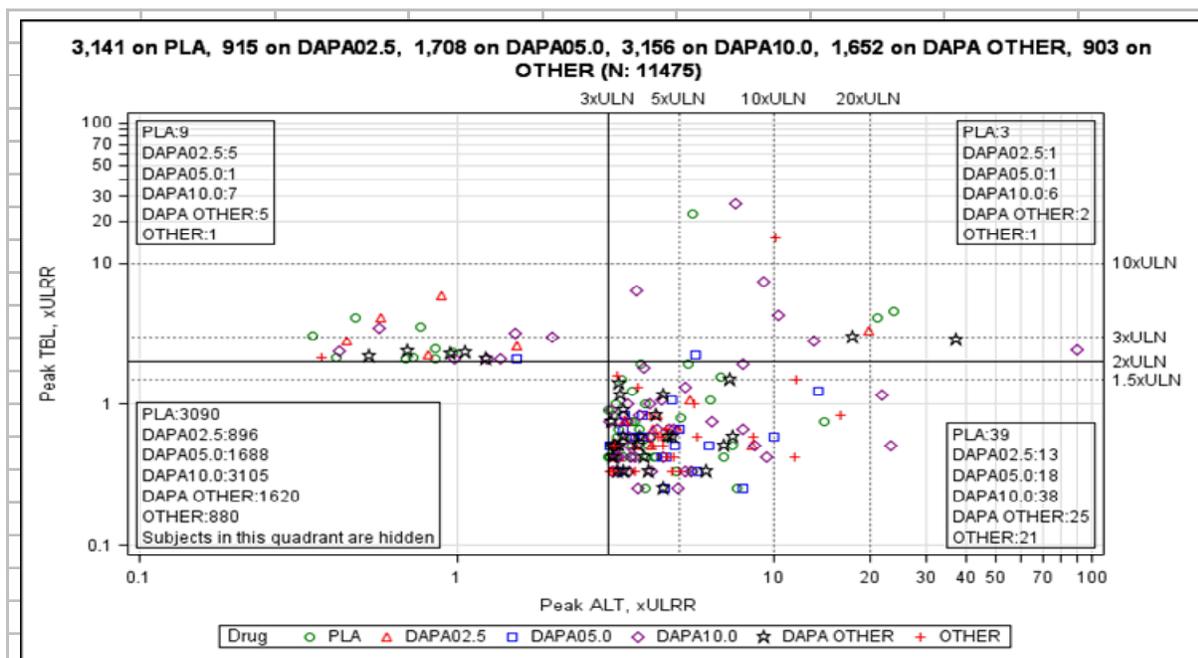
This case was of major importance, along with concerns about bladder and breast cancer, in deciding upon the Complete Response decision rendered in January 2012. The sponsor then did further analyses and observations, with additional cases started and followed, leading to the resubmission of 11 July 2013. Let us first consider what happened to the case of concern.

Case 4-4402-6, the Indian man living and followed in the UK at site 4402, is now 84, and is still being followed more than 5.5 years since he started dapagliflozin, and almost 5 years since it was stopped. He has continued to have smouldering liver disease with occasional flares, and has been treated with azathioprine and occasional steroids for autoimmune hepatitis. The most recent data on liver tests was on 11 January 2012, 18 months before the resubmission of NDA 202293. Consultations were requested from Drs. Paul Watkins and Willis Maddrey, who had much more data than did Dr. Seeff or the other consultants when the NDA was originally submitted in 2011, as stated in the Hepatic Adjudication Report of 13 June 2013.. With the much longer follow-up and clinical responses to treatment, it has become clear that the patient has autoimmune hepatitis. Whether it was coincidental that the first serious manifestation was triggered by exposure to dapagliflozin is controversial, and is complicated by his low-grade underlying hemochromatosis.



The above graphic plot of the time course clearly shows recurring peaks of liver inflammation not associated with dapagliflozin, and characteristic of autoimmune hepatitis. The graphic plot submitted by the sponsor, in the Hepatic Adjudication Report of 19 June 2013 is very similar, although the sponsor's graph showed many more data dates than were reported to us.

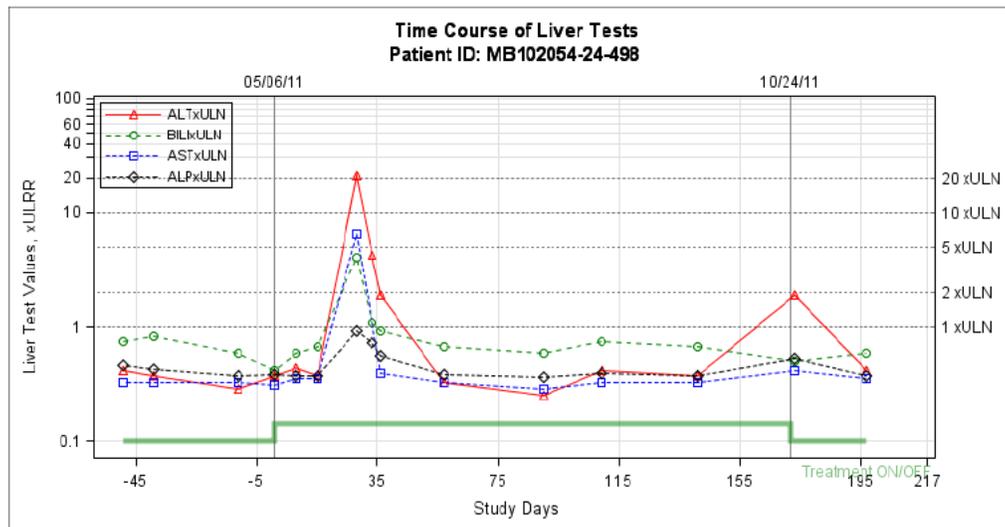
The sponsor submitted a series of incremental datasets for entry into eDISH by Dr. Guo, but only the latest labeled by the sponsor as DAPN95 will be considered. There were 4,993 subjects who were added, of whom 2918 were on various doses of dapagliflozin, and 2077 on comparators. The eDISH step 1 graph below contains a total of 11,475 subjects (10,279 of whom were in the left lower quadrant of normal or nearly normal peak ALT and TBL values, and are "hidden" to reduce the huge computer memory for so many people's data).



It may be noted that there were 28 subjects who showed some TBL elevation but no ALT rise of significance at any time they were observed (left upper quadrant). There were considerably more who showed ALT peak elevations at some time, including two >20xULN and six >10x but <20xULN, with no rise in TBL (right lower quadrant). The subjects of greatest clinical interest were the 14 in the right upper quadrant who had evidence of both hepatocellular injury (ALT>3xULN) and liver dysfunction (TBL>2xULN), for whom individual attention was directed to determine whether the abnormal serum chemistries indicated drug induced liver injury (DILI) or if the findings were explained by some other cause. Each of them had a full time course plot of all the liver test data available during their observation (step 2 of the eDISH program), and review of narrative clinical information that might give clues to the diagnosis (step 3 eDISH program). Of the 14 subjects, 10 had been evaluated before in the previous submission, and only one subject, the Indian man studied in the UK (#04-4402-6) was of concern (right-most star ALT 38.9 xULN and TBL 3.0 xULN in the right upper quadrant). It had been thought, on the basis of available data at the time of the 2011 submission, that he might have serious DILI because of his response that followed dapagliflozin 2.5 mg/day for about six months, as was concluded on review by Dr. Leonard Seeff. The sponsor's consultants had mixed opinions on whether it should have been diagnosed as autoimmune hepatitis or DILI (see above). The current resubmission provided an extra two years of clinical follow-up information that showed recurring flares and continuing hepatic inflammation despite azathioprine, more characteristic of autoimmune hepatitis, as was concluded by Drs. Maddrey and Watkins who were consulting for the sponsor.

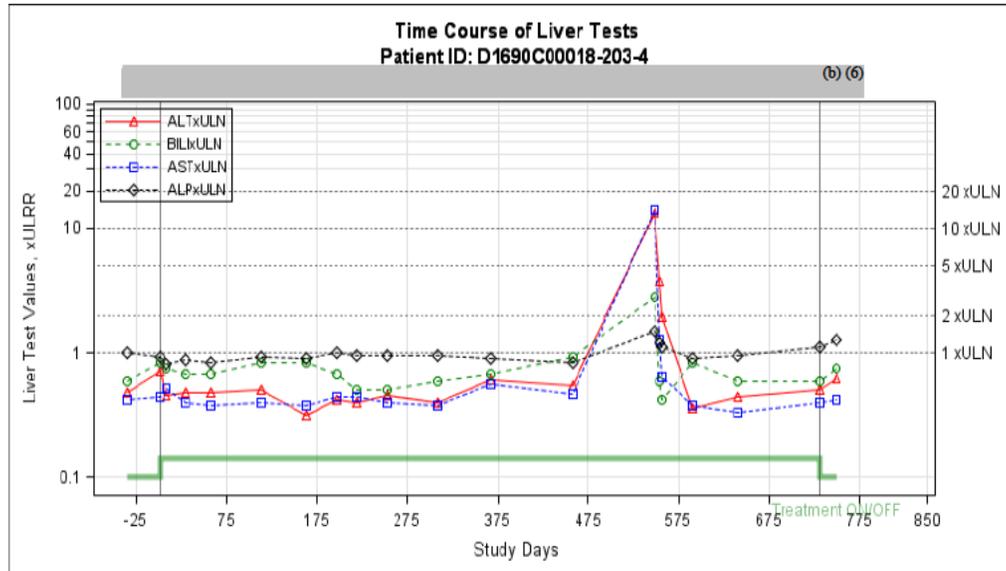
For the four cases newly reported in the resubmission, we show below the time courses of the liver tests, although no narrative clinical information was submitted for the eDISH analyses. However, the Hepatic Adjudication Report did provide sufficient additional information tghat it was possible to conclude that none of them had serious DILI due to dapagliflozin. One the subjects had been randomized to placebo (MB102054-24-498), and the other three randomized to dapagliflozin 10 mg/day (D169000018-203-4, D169000018-201-8, MB102077-66-70996). Each of them is shown in the time course eDISH step 2 graphs below:

MB102054-24-498 was a Chinese man aged 63 randomized to placebo addition on 6 May 2011, and showed a prompt rise in ALT to 21.2 xULN, AST 6.5 xULN, TBL 4.1 xULN, but ALP not elevated:



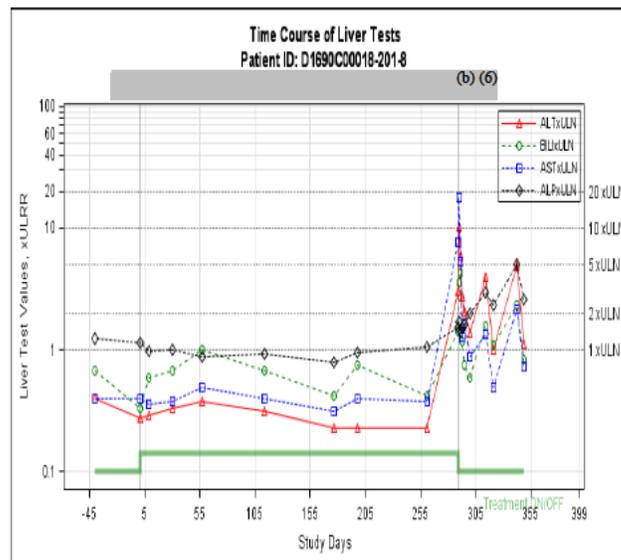
Comment: According the information in the Hepatic Adjudication Report (HAR) page 354-5, the subject had a history of cholecystitis but tested negative for viral hepatitis B and C bt serology before starting the study. He reported an upper respiratory infection on Day 26 and took 1 g of acetaminophen two days in a formulation containing dextromethorphan, pseudoephedrine, and chlorpheniramine, but no herbal products. On Day 28 he had anorexia and fever and elevated ALT, AST and TBL, all were transient and returned to normal promptly despite continuing study medication, which turned out to be placebo. No other explanation was for the moderate test abnormalities was found, and the investigator did not think them related to study medication. The Hepatic Adjudication Committee, consisting of consulting Drs. (b) (4) all of whom I know well and respect), plus AstraZeneca Dr. (b) (4) and Bristol-Myers Squibb Dr. (b) (4), agreed that it was unlikely that the study medication has caused the effects reported. Their conclusion seems correct to me, also.

Let us now look at the cases that occurred in subjects randomized to dapagliflozin 10 mg/day: **D169000018-203-4** was an obese (BMI 32.0) Argentinian man aged 70 who was randomized to add 10 mg/day dapagliflozin (b) (6). All of his liver tests remained in the normal range for over a year and a half, then on Day 549 suddenly rose sharply ALT 13.4 xULN, AST 14.0 xULN, ALP 1.5 xULN, and TBL 3.4 xULN (see HAR, pages 279-81)



Comment: The patient, now 72, had a history of gallstones. Ultrasound examination on Day 550 showed multiple gallbladder stones. He was not hospitalized, but was treated with scopolamine and the liver test abnormalities subsided despite continuing dapagliflozin. Cholecystectomy was done on Day 623, and he completed the study on (b) (6) (Day 737).

D169000018-201-8 was an overweight but not obese (BMI 28.2) Argentinian man aged 70 who started dapagliflozin 10 mg/day (b) (6). He developed right hypochondral and epigastric pain, nausea and vomiting on Day 289, and study medication was stopped.

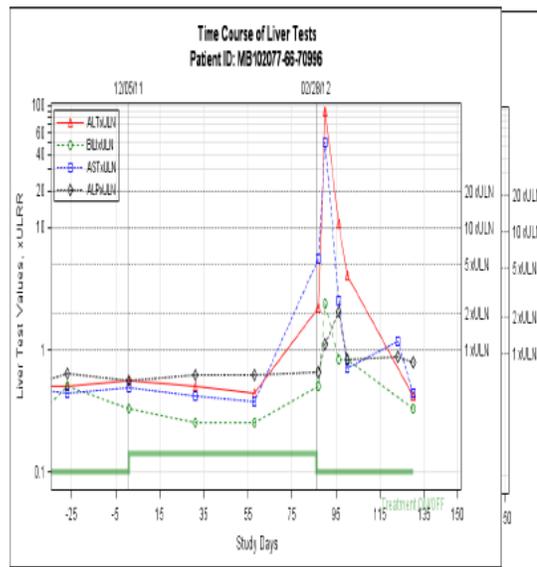


His ALT was sharply elevated to 3.1xULN, AST 7.7xULN, ALP 1.5xULN and TBL 1.4xULN on Day 289, done because of the symptoms. The elevated values peaked within two days at ALT 10.3xULN, AST 18.0xULN, ALP 5.0xULN and TBL 4.3 xULN, then rapidly declined. Ultrasound study on Day 290 showed no biliary ductal dilatation, and repeat test in Day 293 showed fatty liver and pancreatic infiltration. He was discharged from hospital on Day 297, but elevated chemistry tests

were slow to resolve entirely, showing fluctuations but no symptoms, and were not quite normal on Day 349 ^{(b) (6)}: ALT 1.1xULN, ALP 2.6xULN, according to information in the HAR pages 275-7. Computed tomography on Day 360 showed thickening of the gall bladder wall, corresponding to an inflammatory process, The finding were adjudicated as unlikely to have been caused by dapagliflozin.

Comment: The patient tolerated dapagliflozin for 36 weeks without indication of abnormal liver test results, then suddenly had both symptoms and test elevations clinically suspected to be due to biliary tract disease but not very well proved.

MB102077-66-70996 was a 57 year-old Indian male who started dapagliflozin 10 mg/day on 5 December 2011. After normal test values at one and two months, he showed elevated ALT to 2.2xULN and AST to 5.5xULN on Day 87. Testing showed that he had hepatitis E (HAR pages 363-4), and he promptly developed mild fever, treated only with acepaminophen, but the serum enzyme values peaked on Day 90 at ALT 89.9xULN and AST 50.4xULN, TBL 2.4xULN then subsided to normal by Day 130.



Comment: This was clearly not a drug-induced problem but an acute viral infection (E) that is fairly prevalent in India. I agree with the actions of the investigators and opinion of the HAC that concluded this was almost certainly due to viral hepatitis E and not dapagliflozin-induced.

The four new cases, like nine of the ten previously considered cases who showed both ALT >3xULN and TBL >2xULN, all had other diagnoses that were considerably more likely than dapagliflozin to have caused the test abnormalities and sometimes symptoms shown. There has been found no increase in minor ALT elevations of no clinical consequence due to study drug. We are left with the case of the Indian man, now 84, living, well studied and treated in the UK at site 4402. The extra two years of follow-up and treatment suggest that he does have autoimmune liver disease, with a rather typical fluctuating chronic course not fully suppressed by azathioprine but quickly suppressible by prednisone. Whether or not this was really caused by dapagliflozin, or if coincidental in its acute onset, has been a divided opinion among expert hepatologists. Dr

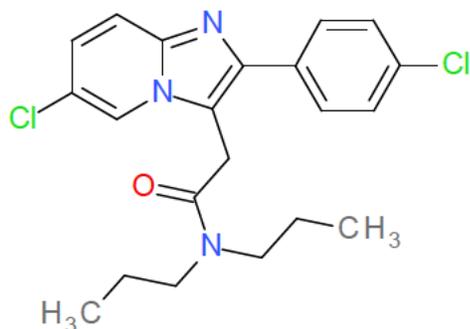
Seeff, with limited early information, concluded that the liver test abnormalities were caused by dapagliflozin, at least probably, but autoimmune disease was distinctly possible. Drs. Maddrey and Watkins, equally qualified and distinguished, reached the opposite conclusion, that it was probably autoimmune disease, but possibly dapagliflozin induced, with more information over a longer term. They all may be probably right to some degree. It cannot be determined with great certainty that no liver disease ever would have occurred in this man if he had not been treated with the low dose of dapagliflozin, nor can it be assumed that the acute autoimmune hepatitis would have begun at that exact time if he had not been started on dapagliflozin just before that time. Suspicion remains, but the effect of the autoimmune liver disease that has become clearer in retrospect with the longer follow-up has not been seriously disabling, and he is getting to a ripe old age despite it. It looks very much like the dapagliflozin did something to this man's liver that was suppressed quickly by steroid treatment, but left behind a chronic autoimmune hepatitis that persists long after any traces of dapagliflozin can be playing a role. It is not a clean yes/no diagnosis, and the possibility of very rare dapagliflozin-induced initiation of a chronic disease cannot be excluded.

The issue of drug-induced autoimmune hepatitis (DIAIH) has been debated in the literature for many years. Bjornsson and a group of Mayo Clinic hepatologists discussed this question at some length (2010 June), concluding that a significant portion of patients with AIH were drug-induced and particularly by nitrofurantoin or minocycline. That article triggered four responses to the journal (*Hepatology*), and Sugimoto and colleagues in November 2011 added seven more cases from Japan they thought were caused by five other drugs (ofloxacin, dlclofenac, benzbromarone, cefachlor, loxoprofen) or herbal products). Liver biopsy does not reliably make the differential diagnosis, despite very careful work and consensus of expert hepatic pathologists (Suzuki et al. 2011) who used as their standard of DILI a series of cases from the Spanish group at Malaga that has itself been troubled (Lucena et al. 2011) by issues about correct diagnosis of autoimmune hepatitis and DILI. Others (Manns et al, 2010) have dodged the issue when writing international guidelines for the diagnosis and treatment of AIH. As far as being confident that a distinction can be reliably between DILI with autoimmune features and DIAIH, the world simply isn't there yet.

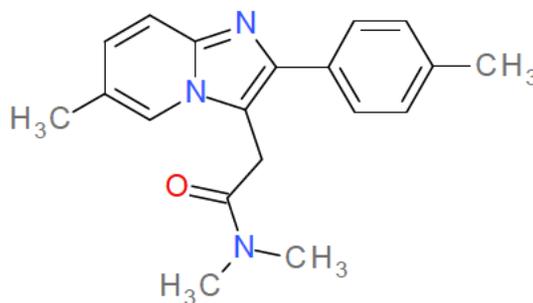
If dapagliflozin may have caused, or possibly caused, at least one case of serious DIAIH, and raised concerns about many more cases of lesser clinical severity, enough to delay its approval, the first synthetic SGLT2 inhibitor, why and how may it be different from its successor cousin, canagliflozin, that was developed later and approved earlier with no serious liver toxicity found in almost as many patients treated for the same disease and internationally on approximately the same range (10,730) of patients studied and treated? (b) (4)

The answer is that we don't know. It may be of interest to look at the molecular structures of the three -gliflozins (see figure on page 3, above). Please note that they are remarkably similar, and that all differ from the natural product phlorizin by the removal of the oxygen atom linking the D-glucose to the synthetic side chain, and that the nearby phenyl group in both dapagliflozin and empagliflozin has a chlorine (-Cl) atom para (4) to the link (1) to the glucose, with slightly different side chains at the meta (3) link. Canagliflozin instead has a methyl (-CH₃) group at the para (4) position. Does that matter? I am certainly no expert in molecular structural effects on how the molecules react or are metabolized, but it may be recalled that (b) (4)

(b) (4) alpidem (Anaxyl®, Synthelabo, now Sanofi-Aventis) marketed in France in 1991 but never approved in the United States, Alpidem was an anxiolytic drug that had to be withdrawn from the French market in 1994 because it caused severe hepatotoxicity. A demethylated analog, zolpidem (Ambien®, and many other trade names) was developed by the same company and was approved in the United States 2 September 2005 (NDA 021774) for treatment of insomnia. The metabolic differences between the two compounds were studied by Berson et al. (2001), a group that included Dr. Dominique Pessayre, one of the sponsor's hepatic injury adjudicators.



alpidem (ANAXYL)
hepatotoxic !



zolpidem (AMBIEN)
not hepatotoxic

The sponsor's glowingly enthusiastic backgrounder document (128 pages) was submitted 4 November 2013, in preparation for the Advisory Committee meeting scheduled for 12 December 2013. In a short paragraph on page 11 in the executive summary, it totally dismisses the liver problem based on the re-diagnosis of the case #4-4402-6 as autoimmune hepatitis by their two new consultants, Dr. Willis Maddrey and Paul Watkins. In more detail, the case is reviewed on pages 86-7, in which they cite the Bjornsson paper with the Mayo group (2010) and one of the many papers on autoimmune hepatitis by A. J. Czaja, who has published 195 articles on the topic of autoimmune liver disease or hepatitis since his first in 1983, or an average of one every two months for 30 years. Thinking is changing about this most difficult diagnosis, and these recent opinions may not be final. Drug-induced liver disease is not one single entity but many diseases with different manifestations that can mimic any liver disease of any etiology. It is premature to close on the definition of DIAIH as totally distinct from AIH or other forms of DILI. The clear difference between pure AIH, if there is any such thing, and DIAIH may be so, but is still not generally accepted.

There is reason to be a little cautious, if it is decided to approve this drug

(b) (4)

The labeling for dapagliflozin should reflect the concerns that have been held for it during the careful review by DMEP, and patients should be warned of those concerns. There is no good justification for requiring any periodic monitoring, as by monthly ALT testing, but patients optimally should be warned to report any early symptoms of possible liver injury or dysfunction

(such as anorexia, fatigue, nausea, dark urine, vomiting, yellowish sclera, right upper, epigastric or other abdominal discomfort) to their physicians immediately, and interrupt taking these agents while investigation is done to find out whether the minor symptoms are being caused by injury to the liver or not, how it is changing over time during close observation, and thorough immediate investigation for cause, with appropriate treatment. That is simply good medical practice, and not meant to dictate how medicine should be practiced, but busy physicians do not have the time to distinguish fine points of difference between these very similar and new drugs; advice to them should come from careful medical reviewers rather than from salesmen.

Copies of references are available on request. Further commentary and follow-up consultation will be sent after data from completed and reported phase II studies have been received, entered into eDISH, and evaluated. I shall be pleased to attend the meeting of the Advisory Committee in December, to answer any questions if they arise. Your assistance has been much appreciated in the work of this consultative review.

John R. Senior, M.D.

cc: OSE 2013-1922
J-M. Guettier, DMEP
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/s/

JOHN R SENIOR
11/11/2013

Clinical Consultation

FROM: Genevieve A. Schechter, MD
Medical Officer, DOP1

THROUGH: Amy McKee, MD
Clinical Team Leader, DOP1

TO: Dr. Frank Pucino
Division of DMEP
CDER/FDA

SUBJECT: Dapagliflozin and Breast Cancer

DATE CONSULT RECEIVED: September 10, 2013
DATE CONSULT COMPLETED: September 20, 2013

MATERIAL RECEIVED FOR REVIEW:

Initial information which was provided included 13 cases reports for patients who developed with breast cancer along with a consult request to discuss the risk of breast cancer with the use of dapagliflozin (DAPA). On September 11, 2013 DOP1 requested background information from all randomized controlled clinical trials in which dapagliflozin was used to include information regarding sample size, number of patients per arm, the control therapy, incidence of breast and bladder cancer /arm on each trial in order to make an assessment as to risk of these cancer. Dr. Pucino, the DMEP reviewer completed a table containing this information and confirmed the accuracy of the information with the applicant (BMS-Astra Zeneca). In addition, Dr. Pucino provided links to the 30-Month Update and the patient narratives. The information was received on September 17, 2013. Dr. Pucino was advised that the consult could not be completed by the requested date of September 22, 2013 due to the delay in obtaining all of the information necessary to make a risk assessment.

Requested Action: DMEP requested review and input from OHOP regarding:

- 1) The significance of the observed imbalance in incidence of bladder and breast cancers in the pooled Phase 2b and 3 controlled clinical trials, and perspective on the expected background incidence of these malignancies
- 2) The likelihood of the study drug contributing to the observed imbalance
- 3) Any additional advice or recommendations that OHOP has to offer.

[Dr. Ning will review bladder cancer information. Dr. Schechter will review breast cancer information.]

Consultant Review:

Review of Cases: Case reports for thirteen patients who developed breast cancer on study were provided for review. Ten cases were on the dapagliflozin arm and three cases were on the placebo arm. The age range of patients on the dapagliflozin arm is from 53-73 years with a median age of 60.5 years while on the control arm, the three patients

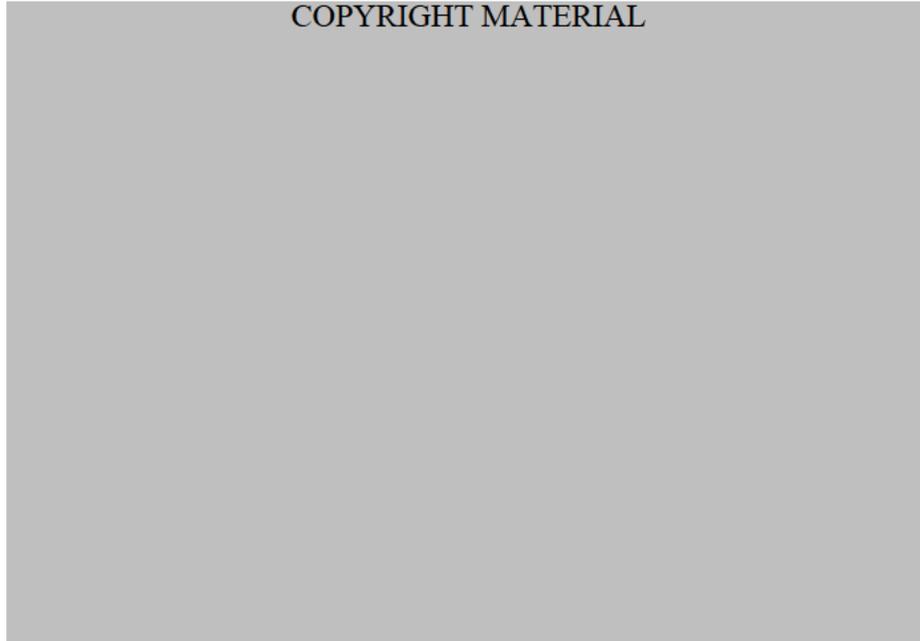
were 64, 69, and 74 years old. For the ten patients on the dapagliflozin arm, time from diagnosis of Type II Diabetes ranged from 6 months to 26 years with a median time from diagnosis of 7 years. For the three patients on the control arm the time from diagnosis is reported as 3, 6, and 20 years. Median duration of DAPA therapy for the pooled RCT group was 336 days with a mean duration of 384 days while on the control arm the median is 337 days with a mean of 390 days. Review of individual patient narratives for 13 patients revealed the following information. Two patients (D1690C00006-1403-2, MB102021-59-482) on the DAPA arm were diagnosed with invasive ductal breast Cancer on Study Day 6 and Study Day 16 respectively. These two cancers are considered unlikely to be related to DAPA therapy. The time of first detection of the 8 breast cancers (Day 6 and Day 16 cases excluded) on the DAPA arm ranged from Study Day 113 to Study Day 334. Two cancers, a multifocal lobular carcinoma and an invasive ductal carcinoma, were diagnosed with mammography on Day 244 and Day 264 respectively. Stage could be determined in eight of ten cases in the DAPA arm and included 1 case of DCIS, two Stage 1 invasive ductal carcinoma, five Stage II breast cancers with four invasive ductal cancer, and one invasive multifocal lobular carcinoma. On the control arm one case of DCIS and two cases of invasive ductal carcinoma (one with DCIS) were reported. In seven of ten cases on the DAPA arm, the tumors were ER+ positive; in one case hormone receptor status was negative, and for two cases receptor status was unknown. Three cancers were reported to have high grade (Grade 3) histology, four Grade 2 histology, one Grade 1 histology, and for two cancers no Grade was reported. On the placebo arm one Grade 2 and two Grade 1 breast cancers were reported. Of the ten cancers on the DAPA arm two were HER2+, five were HER2-, and the HER2 status was unknown in three cases. On the placebo arm one was HER2+ and in two the status was unknown. With regard to mammographic screening only three patients appear to have been screened regularly. As noted about two patients were diagnosed by mammography.

Other Applicant Information: In the 30 Month Update, NDA Resubmission pooled data from the 21 completed Phase 2b and 3 randomized trials, the reported incidence of all neoplasms (benign and malignant) is 89 cases on the dapagliflozin arm and 51 cases on the placebo arm. According to the applicant, the incidence of breast cancer on the dapagliflozin arm was 0.2% (12/5936), while on the control arm the incidence was 0.1% (2/3402) using the pooled data. At the data cutoff for the 30 Month Update, the applicant notes that the incidence rate ratio vs. control for breast cancer was 2.472 [95% CI 0.636, 14.095]) and has not changed substantially since the Major Amendment submitted on 11/20/2011, at which time the incidence rate ratio was 1.903 [95% CI =0.461, 11.230]). The applicant notes that the incidence ratio continues to be lower than the incidence rate observed (4.406 [95% CI = 0.570, 200.86]) on 05/12/2011, the time point at which the data cut was made in preparation for the first Advisory Committee Meeting for dapagliflozin.

Information about Breast Cancer Incidence: With regard to the breast cancer incidence, the worldwide incidence of invasive breast cancer in developed countries for 2008 is reported as 71.1cases/100,000 female population (0.07%) while in under-developed countries with incidence is reported as 29.3/100,000 female population (0.03%) with the overall incidence of 42.3 new cases/100,000 female population (0.04%). The highest incidence worldwide is reported for North America, Argentina, Western

Europe and Australia where the reported incidence is 80+ cases/100,000 female population (> 0.08%).¹

SEER data collected from 2000-2009 shown in Figure 1 below provides the estimated incidence of all breast cancer over nine year period for Non-Hispanic White (NHW) women, Non-Hispanic Black (NHB) Women, Asian Women, and Hispanic (Hisp) women in the US.²



The incidence of breast cancer for Non-Hispanic White ranged from 246.9 cases/100,000 women to a low of 228.8 cases/100,000 women in 2005 with an increase to 240.6 cases /100,000 women over this period or an incidence of 0.21-0.24%. For Non-Hispanic Blacks the number of cases/100,000 women during the period from 2000-2009 ranged from 206.0 to 224.9 cases for incidence of 0.21% to 0.22% over this nine year period. For Asian the incidence of breast cancer increased from 0.16% to 0.18% (160 cases -180 cases/100,000 females over the nine year period reflecting an increasing incidence over the nine year period. The incidence of breast cancer was stable in Hispanic women at about 0.15% (150 cases/100,000 women).

Information on Breast Cancer and Diabetes: The occurrence of breast cancer in the diabetic women enrolled on these studies is not unexpected. The incidence of breast cancer in patients with Type II diabetes is increased as compare to the general population. A recent meta-analysis of breast cancer incidence in diabetic women as compare to non-diabetic women estimated a Hazard Ratio (HR) of 1.23 (95% CI: 1.12, 1.34). Breast cancer mortality is also increased in Type II diabetics with an estimated

¹ Youlden, Danny R. et al. "The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality". *Cancer Epidemiology* (2012) 36:237-248.

² Hou, Ningqi et al. "A trend analysis of breast cancer incidence rates in the United States from 2000 to 2009 shows a recent increase". *Breast Cancer Res Treat* (2013) 138:633-641.

(HR=1.38 [95% CI: 1.2, 1.58]) for unknown reasons.³ The median age on the pooled dapagliflozin studies is 58 years on the DAPA arm and 59 years on the placebo arm. About 89% of new breast cancer cases are diagnosed after age 40 and the incidence of breast cancer increases with age.⁴ Based on the median (mean) age reported on the dapagliflozin-treated population and the control population, the finding of breast cancer cases is not unexpected but does not explain the imbalance between arms. Information has been published to suggest that use of metformin reduces the risk of all cancers while sulfonylurea usage may increase cancer risk based on data from randomized controlled trials. Analysis of 24 metformin studies in patients with Type II DM showed that metformin use is associated with reduced risk for the development of cancer in cohort studies (RR=0.70[95% CI=0.67–0.73]) and case–control studies (OR=0.90 [95% CI=0.84–0.98]), but this finding was not supported by data by randomized clinical trials (RR=1.01[95% CI=0.81–1.26]). Data from 18 sulfonylurea studies in subjects with Type II DM showed that sulfonylurea use is associated with an increase in all cancer risk, in cohort studies (RR=1.55 [95% CI=1.48 -1.63]), though data from RCTs (RR=1.17[95% CI=0.95–1.45]) and case–control studies (OR=1.02 [95% CI=0.93–1.13]) failed to demonstrate a statistically significant effect.⁵ Further analysis of large clinical trials is needed to determine if metformin does indeed reduce the cancer risk and if sulfonylureas increase cancer risk. In addition, use of other medication such as statins for management of hyperlipidemia, a condition that occur commonly in diabetics, has been reported to reduce cancer risk.

Information on Drug Class and Breast Cancer: Review of the application for canagliflozin (Invokana®) reported that in preclinical studies an increase in renal tubular adenomas, Leydig cell tumors, and pheochromocytoma were seen. The increase in Leydig cell tumors is thought to be related to increased LH-RH secretion. A post-marketing requirement (2027-3) to observe using post-marketing and domestic spontaneous report of malignancy is in effect with yearly interim reports starting in May, 2013 and the final report due in November, 2023. No increase in bladder or breast cancer was observed with canagliflozin. Pre-clinical studies conducted by the applicant appear to rule out a tumor promoting effect for dapagliflozin.

Discussion and Conclusion: Ten cases of breast cancer occurred on the dapagliflozin arm. Two cases are eliminated due to detection of breast cancer on Day 6 and Day 16 of study so that the incidence is about 0.13%. Three cases of breast cancer were reported on the placebo were observed for an incidence 0.08%. The incidence of breast cancer observed on the pooled data from the randomized clinical trials conducted to study dapagliflozin is consistent with the incidence observed in the SEER database (0.15-0.23%). While an increased incidence of breast cancer is observed on the dapagliflozin relative to the placebo arm, the decline in the incidence risk ratio over time, the lack of screening mammography prior to study entry coupled with the

³ DeBruin, K.M.J. et al. “Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer”. *Brit. Jour. Surg* (2013) 100:1421-1429.

⁴ Youlden, Danny R. et al.

⁵ Thakkar, Bindiya et al. Metformin and Sulfonylureas in Relation to Cancer Risk in the Type II Diabetic Patients; A Meta-analysis using primary data of published studies. *Metabolism (Clinical and Experimental)* (2013) 62:922-934.

occurrence of the breast cancers within the first year of dapagliflozin therapy, the median time from diagnosis of diabetes of seven years, the history of prior exposure to other oral hypoglycemic agents, and the hormone receptor positivity of the breast cancers suggests that the increased incidence of breast cancer is a spurious finding. Furthermore, there is not enough information in the narratives provided to assess risk factors for breast cancer in each individual patient who was diagnosed with breast cancer. The data with regard to breast cancer risk in association with this drug is inconclusive and insufficient to recommend inclusion in the label. If concerns about a breast cancer risk remain, an applicant-sponsored registry to collect information on breast cancer cases with dapagliflozin use over a prolonged period of time may provide enough additional information to determine if there is increased risk of breast cancer with dapagliflozin use.

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/s/

ALICE KACUBA

10/21/2013

Archiving a pdf clinical consult review.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Review

Date: October 3, 2013

Reviewers: Christine E. Chamberlain, PharmD, CDE, Safety Evaluator
Ali Niak, MD, Medical Officer
Division of Pharmacovigilance I

Team Leaders: S. Christopher Jones, PharmD, MS, MPH
Allen Brinker, MD, MS
Division of Pharmacovigilance I

Deputy Division Director: Min Chen RPh Acting Director
Division of Pharmacovigilance I

Product Names: Dapagliflozin
Invokana® (canagliflozin)

Subject: Postmarketing reports of severe liver adverse events and cancer
(especially bladder and breast cancer)
in patients taking canagliflozin (INVOKANA) and
dapagliflozin

Application Type/Number: NDA 202293 (dapagliflozin)
NDA 204042 (canagliflozin)

Applicant/Sponsor: Bristol Myers Squibb
Janssen Pharmaceuticals

OSE RCM #: 2013-1638

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EXECUTIVE SUMMARY

This review evaluates postmarketing reports in the FDA Adverse Events Reporting System (FAERS) database and medical literature for an association between canagliflozin or dapagliflozin and severe liver adverse events, cancer (especially bladder and breast cancer) and any other potential safety signals identified for these two sodium glucose co-transporter-2 (SGLT2) inhibitors.

A total of 113 FAERS reports were retrieved for canagliflozin and dapagliflozin using a comprehensive search. Only two serious liver adverse events were identified with dapagliflozin (none with canagliflozin) and these cases included concomitant medications known to be potentially hepatotoxic. No breast cancer cases were reported for either drug. Five bladder cancer cases were identified with canagliflozin. Four of the five cases were confounded by either current use or history of smoking tobacco products. After review of diagnosis date we concluded that these bladder cancers are incident cases that are in addition to those reported in the NDA review of canagliflozin prior to approval.

In this DPV review we identified few hepatic adverse events and most of these events included concomitant medications known to be potentially hepatotoxic. No cases of breast cancer were noted with either SGLT2 inhibitor. Bladder cancer cases represented the majority of cancers occurring in canagliflozin treated patients. Bladder cancer is a relatively common cancer in the mature adult population so inference on causality from spontaneous reports is severely limited. There are no other potential safety signals identified for these SGLT2 inhibitors. DPV will maintain surveillance of bladder cancers for SGLT2 inhibitors as a drug class with specific interest in pursuit of more information on cases that might represent rare histologic subtypes.

1 INTRODUCTION

This review evaluates postmarketing reports in the FDA Adverse Events Reporting System (FAERS) database and medical literature for an association between canagliflozin or dapagliflozin and severe liver adverse events, cancer (especially bladder and breast cancer) and any other potential safety signals identified for the sodium glucose co-transporter-2 (SGLT2) inhibitor class. On August 22, 2013 the Division of Metabolic and Endocrine products (DMEP) requested this review since the dapagliflozin NDA is being reviewed for a second cycle under a six month review clock. During the first NDA review cycle a signal of possible liver injury, imbalances in breast and bladder cancer favoring comparator and concerns of modest efficacy relative to safety emerged. The OSE drug induced liver injury (DILI) team is reviewing liver safety of dapagliflozin NDA as part of a separate consult. An advisory committee meeting is scheduled for early December 2013 with a PDUFA goal date of January 11, 2014.

As noted in previous reviews^{1,2,3}, inference on cancer causality from spontaneous reports is severely limited for common cancers. Unless a rare, specific histologic subtype is specified, bladder and breast cancer not otherwise specified are relatively common cancers in mature adult populations. The primary focus of any review of spontaneous reports of common cancers is thus for identification of rare subtypes which may not have been identified in report coding.

1.1 REGULATORY HISTORY

Canagliflozin, the first SGLT2 inhibitor available in the US, was approved by the FDA on March 29, 2013. As of July 2013, dapagliflozin (Forxiga®) is approved in Europe (November 2012), Australia (October 2012) and Mexico (April 2012).

1.2 PRODUCT LABELING

Canagliflozin (Invokana®) has the following adverse drug reactions or adverse events as part of the latest version of FDA approved labeling. The location of this information is shown in parentheses (AR= Adverse Reactions section; WP = Warning and Precautions section).

- Female mycotic infections (AR)
- Urinary tract infections (AR)
- Increased urination (AR)
- Increased LDL-C (AR)
- Hypotension (WP)
- Impairment in renal function (WP)
- Hyperkalemia (WP)
- Hypoglycemia when combined with insulin or insulin secretagogue (WP)
- Hypersensitivity reactions (WP)⁴

¹ Brinker A. Exenatide, sitagliptin, and other anti-diabetics (class), Pancreatic Cancer. OSE RCM # 2009-1704. 10 Dec 2009.

² Brinker A. Exenatide, sitagliptin, and other anti-diabetics (class) Medullary Thyroid Cancer. OSE RCM#2009-1703. 03 Dec 2009.

³ Swann J. Insulin Glargine (Lantus®) Malignancies. OSE RCM #2009-1293. 13 Nov 2009.

⁴ Invokana® (canagliflozin) [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2013.

2 METHODS

2.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 2.1.

Table 2.1. FAERS Search Strategy*	
Date of search	August 26, 2013
Time period of search (FDA received date)	Not specified- August 26, 2013
Product Terms	Canagliflozin, Dapagliflozin as active moiety
MedDRA Search Terms	All PT terms

* See Appendix A for description of the FAERS database.

After this initial search, DPV then screened these reports for any MedDRA preferred term from an HLT or SMQ in Table 2.11 below. Any report containing at least one preferred term within the listed HLT or SMQ was considered a liver or malignancy event of interest.

Table 2.11. MedDRA Terms Used to Identify a Hepatic or Malignancy Report	
	Event Type
MedDRA Search Terms HLTs:	Liver Hepatic and hepatobiliary disorders nec;hepatic and portal embolism and thrombosis;hepatic and portal necrosis and vascular insufficiency;hepatic autoimmune disorders;hepatic enzymes and function abnormalities;hepatic failure and associated disorders;hepatic fibrosis and cirrhosis;hepatic infections (excl viral);hepatic metabolic disorders;hepatic neoplasms malignant;hepatic therapeutic procedures;hepatic vascular disorders;hepatic viral infections
	Malignancy None
MedDRA Search Terms: SMQs	Liver Drug related hepatic disorders - comprehensive search (SMQ)
	Malignancy Breast malignant tumours (SMQ);malignant tumours (SMQ)

2.2 VIGIBASE DATA MINING SEARCH STRATEGY

Since dapagliflozin is approved outside of the United States, DPV searched VigiBase⁵ to identify adverse events reported for the drug. VigiBase is the World Health Organization (WHO) global individual case safety report (ICSR) database system. Our strategy is listed in Table 2.2.

⁵ Lindquist, Marie. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Information Journal. 2008; 42:409-419. <http://who-umc.org/graphics/24965.pdf>

Table 2.2. VigiBase Data Mining Search Strategy			
Data Refresh Date	May 31, 2013		
Product Terms	Dapagliflozin		
Empirica Signal Run Name	Generic Run Q2		
MedDRA 16.0 Search Strategy	All PTs		

2.3 FAERS DATA MINING SEARCH STRATEGY

We searched FAERS using Empirica Signal Data Mining software to detect disproportionately reported events associated with canagliflozin. Below is the search strategy used.

Table 2.3. FAERS Data Mining Search Strategy			
Data Refresh Date	September 23, 2013		
Product Terms	Canagliflozin		
Empirica Signal Run Name	Generic (S)		
MedDRA Search Strategy	All PTs		
Data Refresh Date	September 19, 2013		
Product Terms	Canagliflozin		
Empirica Signal Run Name	Generic (S), HLT		
MedDRA 16.0 Search Strategy	Bladder neoplasms malignant HLT		

2.4 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 2.4.

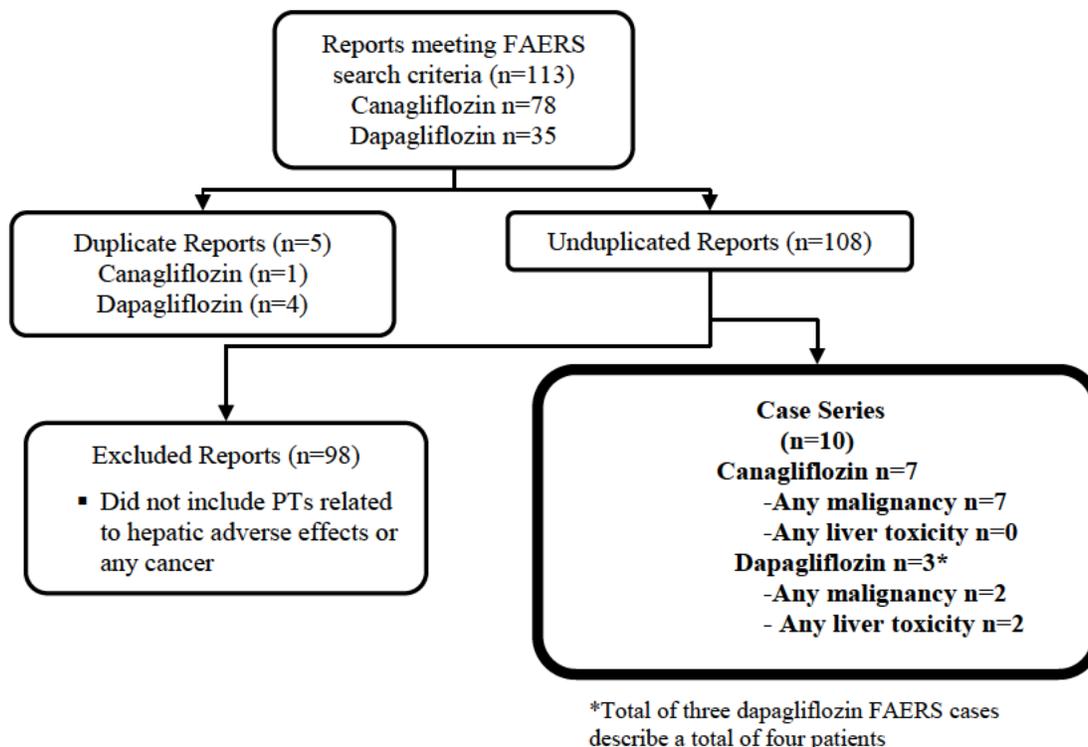
Table 2.4. Literature Search Strategy	
Date of search	September 13, 2013
Database	PubMed
Search Terms	Dapagliflozin, Canagliflozin, cancer, metastasis, neoplasms, prostate cancer, bladder cancer, breast cancer, liver/hepatic cancer, adrenal gland metastasis, bone metastasis, liver/hepatic metastasis, lung metastasis, liver/hepatic failure/cirrhosis, liver/hepatic adverse events, elevated liver/hepatic function tests
Years included in search	Through September 13, 2013
Language	English

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 113 reports. After narrowing the search to hepatic adverse events and malignancies and accounting for duplicate reports, 10 cases were included in the case series of liver adverse events and cancer (especially bladder and breast cancer) reported with canagliflozin or dapagliflozin (see Figure 3.1).

Figure 3.1. FAERS Case Selection



DPV reviewed these ten cases and used the WHO⁶ causality assessment to determine the likelihood that each event was caused by either dapagliflozin or canagliflozin. Section 6.2 Appendix B lists specific details for each FAERS case reporting a liver adverse event or a malignancy (n=10).

3.2 MOST FREQUENTLY REPORTED MEDDRA PREFERRED TERMS (PTs) FOR FAERS REPORTS WITH SERIOUS AND NON-SERIOUS OUTCOMES

Table 3.1 and 3.2 summarize the most frequently reported MedDRA PTs from all reports in FAERS reported with dapagliflozin and canagliflozin, respectively as of August 26, 2013.

Table 3.1. Most Frequently Reported MedDRA Preferred Terms (PTs) with N ≥ 2 for Dapagliflozin (n=31)* received by FDA from January 01, 1965 to August 26, 2013

Event-Preferred Terms(PTs)	Total Cases	Percent of Total
Chest Pain	3	9.68

⁶ The use of the WHO-UMC system for standardised case causality assessment. Accessed from: <http://www.WHO-UMC.org/graphics/24734.pdf> [last accessed on 2013 Sep 12]

Hypoglycaemia	3	9.68
Anaemia	2	6.45
Angioedema	2	6.45
Depression	2	6.45
Fatigue	2	6.45
Inflammation	2	6.45
Peripheral Vascular Disorder	2	6.45
Pneumonia	2	6.45
Pulse Absent	2	6.45
Weight Decreased	2	6.45

* These data have been de-duplicated

Table 3.2. Most Frequently Reported MedDRA Preferred Terms (PT) with N ≥ 2 for Canagliflozin (n=77)* received by FDA from April 1, 2013 to August 26, 2013

Event-Preferred Terms(PTs)	Total Cases	Percent of Total
Urinary Tract Infection	7	11.11
Blood Glucose Increased	6	9.52
Atrial Fibrillation	5	7.94
Diabetic Ketoacidosis	5	7.94
Renal Failure	5	7.94
Dehydration	4	6.35
Nephrolithiasis	4	6.35
Blood Creatinine Increased	3	4.8
Depression	3	4.8
Drug Ineffective	3	4.8
Hypoglycaemia	3	4.8
Incorrect Dose Administered	3	4.8
Off Label Use	3	4.8
Pyrexia	3	4.8
Rhabdomyolysis	3	4.8
Weight Decreased	3	4.8
Abdominal Pain Upper	2	3.2
Adenocarcinoma Of Colon	2	3.2
Blood Glucose Abnormal	2	3.2
Blood Pressure Decreased	2	3.2
Chills	2	3.2
Diarrhoea	2	3.2
Dizziness	2	3.2
Drug Interaction	2	3.2
Fall	2	3.2
Fungal Infection	2	3.2
Gait Disturbance	2	3.2
Myocardial Infarction	2	3.2
Phimosis	2	3.2
Pruritis	2	3.2
Renal Disorder	2	3.2
Renal Failure Acute	2	3.2
Syncope	2	3.2

Transitional Cell Carcinoma	2	3.2
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* These data have been de-duplicated

3.3 VIGIBASE DATA MINING

Table 3.3. VigiBase Data Mining Results with EBGM \geq 2 for Dapagliflozin, by MedDRA Preferred Terms					
MedDRA PT	SOC	N	EB05	EBGM	EB95
Purulent discharge	Infec	2	0.748	3.916	90.125
Peripheral vascular disorder	Vasc	2	0.729	3.348	66.028
Gangrene	Infec	2	0.728	3.318	64.599
Pulse absent	Inv	2	0.727	3.307	64.062
Skin ulcer	Skin	2	0.693	2.568	19.643
Chromaturia	Renal	2	0.684	2.446	9.477
Liver disorder	Hepat	2	0.676	2.354	7.274
Cellulitis	Infec	2	0.656	2.186	5.988
Oedema	Genrl	2	0.636	2.079	5.518
Hepatic enzyme increased	Inv	2	0.636	2.077	5.511
Hypoglycaemia	Metab	2	0.625	2.029	5.337

3.4 FAERS DATA MINING

Table 3.4. FAERS Data Mining Results with EBGM \geq 2 for Canagliflozin, by MedDRA Preferred Terms					
MedDRA PT	SOC	N	EB05	EBGM	EB95
Diabetic ketoacidosis	Metab	5	29.067	68.502	142.151
Urinary tract infection	Infec	8	2.698	5.233	11.712
Hypoglycaemia	Metab	4	1.514	3.855	14.223
Blood glucose increased	Inv	6	1.888	3.81	7.23
Nephrolithiasis	Renal	4	1.41	3.362	7.506
Renal failure	Renal	5	1.513	3.223	6.274
Phimosis	Cong	2	0.748	3.186	56.53
Fungal infection	Infec	3	1.108	3.12	9.743
Transitional cell carcinoma	Neopl	2	0.744	3.088	51.329
Atrial fibrillation	Card	4	1.256	2.911	6.037
Rhabdomyolysis	Musc	3	1.061	2.857	6.896
Adenocarcinoma of colon	Neopl	2	0.726	2.709	28.061
Dehydration	Metab	4	1.127	2.599	5.328
Blood glucose abnormal	Inv	2	0.674	2.165	5.723
Drug interaction	Genrl	3	0.83	2.15	4.791

We conducted an additional search using the HLT “bladder neoplasms malignant.” After review of the narratives of these cases, each represented a case also retrieved in the case series.

Table 3.4.2. FAERS Data Mining Results with EBGM \geq 2 for Canagliflozin, by MedDRA HLT

HLT	N	EB05	EBGM	EB95
Bladder neoplasms malignant	3	1.369	7.964	34.6

3.5 LITERATURE SEARCH

Using the search strategy noted in Table 2.4, no articles (case reports or observational studies) were obtained that addressed any of the search terms. The articles that did mention dapagliflozin or canagliflozin were either basic science articles that addressed mechanism of action (efficacy) rather than safety, or were clinical summary articles outlining the drug’s development plan, or articles which summarized currently labeled information. No new adverse events or any issues related to cancers, metastasis, or liver/hepatic adverse events were noted in the literature search.

4 DISCUSSION

4.1 ADVERSE EVENTS ASSOCIATED WITH DAPAGLIFLOZIN

Overall, there were limited reports in the FAERS database with regards to any cancer or hepatic adverse events reported with dapagliflozin. A comprehensive search of the FAERS database yielded 31 unduplicated reports for dapagliflozin. DPV identified three reports that described some type of cancer or hepatic adverse events in four patients (see Appendix B). Subsequent review of these cases revealed that each originated from a blinded clinical study. Notably, blinding in these cases was maintained, thereby making any causality assessment impossible until the blind is broken (see Appendix B, Dapagliflozin Table, Clinical Trial Column).

Although there were two cases of malignancy reported with dapagliflozin there were no cases of bladder or breast cancer. In the two subjects experiencing malignancy, one developed both prostate cancer and hepatocellular carcinoma (HCC) four months and seven months respectively after study drug was initiated and the second subject developed liver cancer. These are common cancers for this age group and associated risk factors.^{7,8}

The two cases of dapagliflozin liver events were serious in that one case resulted in hospitalization and the other resulted in death. However, the liver adverse event case resulting in death was confounded by baseline elevated transaminases prior to study drug initiation; additionally the event listed as “hepatic failure” occurred after a serious infection (bilateral pneumonia) which included treatment with an antibiotic (clarithromycin) known to cause liver toxicity. The other serious liver adverse event case could be considered possibly related to the blinded treatment regimen, however, this case included the use of levofloxacin, pravastatin and Niaspan, which are all plausible hepatotoxins. Furthermore the event was temporally associated with levofloxacin initiation.

⁷ SEER Stat Fact Sheets: Prostate Cancer. National Cancer Institute Web site. Bethesda, MD. <http://seer.cancer.gov/statfacts/html/prost.html>, Accessed September 27, 2013.

⁸ Cancer Topics: General Information about Adult Primary Liver Cancer. National Cancer Institute Web site. Bethesda, MD. <http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional>. Accessed September 27, 2013.

DPV also conducted a search in VigiBase to detect disproportionate reporting of adverse events from countries where dapagliflozin is currently marketed. We used VigiBase to compute empirical Bayesian geometric means (EBGM) with 90% confidence intervals grouped by all MedDRA PT terms for dapagliflozin. A small number of events were available for data mining. Duplicate data are possible in these scores. Although DPV identified preferred terms for ‘liver disorder’ and ‘hepatic enzyme increased’, we are unable to assess whether these events are serious due to lack of narratives with VigiBase cases. Additionally, there were no malignancy related preferred terms and no new signals identified from this data source.

4.2 ADVERSE EVENTS ASSOCIATED WITH CANAGLIFLOZIN

Adverse events with canagliflozin are of interest in the NDA review of dapagliflozin since canagliflozin is structurally related to dapagliflozin. A comprehensive search of the FAERS database for reports with any cancer or liver adverse event yielded 77 unduplicated reports for canagliflozin. DPV identified seven reports describing any cancer and no hepatic adverse events (See Appendix B). Subsequent review of these cases revealed that each report originated from clinical study 2843175 DIA 3008. Each of these patients was randomized to canagliflozin treatment.

Among the cancer reports, seven patients were noted to have eight cancers (five bladder cancers, two adenocarcinoma of the colon and one renal cell carcinoma). There were no cases of breast cancer identified in FAERS. After assessing the bladder cancer reports, four were not further characterized beyond “urothelial carcinoma” or “metastatic bladder cancer” while one was described as a *nested* variant of urothelial carcinoma. Urothelial carcinoma nested variant is a rare, aggressive neoplasm, often invasive that can infiltrate muscle and perivesical fat.⁹ This variant is challenging to recognize and is associated with persistent and recurrent disease. Additionally, four of the five cases were either current users or had a history of smoking tobacco products, a known risk factor for bladder cancer.¹⁰ Since increased urinary tract infections and glucosuria occur with canagliflozin, and the former has been linked to bladder cancer, we cannot exclude the possibility of canagliflozin accelerating or promoting an oncogenic process. Alternatively, hyperinsulinemia, an active component of type 2 diabetes, alone has been suggested as a risk factor for cancer.¹¹

DPV used Empirica Signal to assess disproportionate FAERS reporting of liver adverse events and any malignancy (see Table 3.4). Duplicate data are possible in these scores. EBGM scores ≥ 2 were selected to improve sensitivity of the data mining results. DPV identified preferred terms for transitional cell carcinoma and adenocarcinoma of the colon with EBGM scores (see Table 3.4) of greater than two, however the confidence interval was wide due to small number of reports. A majority of the preferred terms identified as a result of the search were related to labeled events or the underlying disease and no preferred terms related to liver adverse events were identified. Renal related events are of interest due to hypovolemia and decreased blood pressure, which are known adverse events associated with canagliflozin use.

4.3 DAPAGLIFLOZIN AND CANAGLIFLOZIN PREFERRED TERMS

DPV screened the most frequently reported MedDRA preferred terms for dapagliflozin and canagliflozin (Tables 3.1 and 3.2). In assessing these terms, we conclude that these were either labeled events, related to the underlying disease or were not biologically plausible based on current knowledge of SGLT2 inhibitors.

⁹ Wasco MJ, Daignault S, Bradley D, Shah RB. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Human Pathology*. 2010;41:163–171.

¹⁰ Wu X, Ros MM, Gu J, Kiemeny L. Epidemiology and genetic susceptibility to bladder cancer. *BJU International*. 2008;102:1207-1215.

¹¹ Gallagher EJ, Leroith D. Diabetes, antihyperglycemic medications and cancer risk: Smoke or fire? *Current Opinion in Endocrinology, Diabetes and Obesity*. 2013; 20:5 (485-494).

5 CONCLUSION

In this DPV review, we identified few hepatic adverse events and most of these events included concomitant medications known to be potentially hepatotoxic. No cases of breast cancer were noted with either SGLT2 inhibitor. Bladder cancer cases (n=5) represented the majority of cancers occurring in patients treated with canagliflozin and data mining results indicate disproportionate reporting for bladder cancer. A majority of these cases were urothelial carcinoma, a common histologic type, with one case reported as “nested variant,” a rare subtype. Four of the five cases reported current or prior tobacco use. There are no other potential safety signals identified. Given the limitations of spontaneous reporting for common cancers, it is difficult to draw inference of causality from these cases. DPV will maintain surveillance of bladder cancers for SGLT2 inhibitors as a drug class with specific interest in pursuit of more information on cases that might represent rare histologic subtypes.

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. FAERS CASE SERIES SUMMARY AND WHO CAUSALITY ASSESSMENT

DAPAGLIFLOZIN CASES										
Case # Version Rec'd Date	PTs	Age Yrs	Sex	Case Summary	Time to Event Onset (days)	Confounders	Outcome	Reviewer Comments	Clinical Trial	Causality score WHO
6959184 (9) 4/2/09	Prostate Cancer Hepatic Cancer,	60.75	M	121 days after starting dapagliflozin patient was diagnosed with moderate/grade 2 prostate cancer with a PSA of 17.5ng/ml and bilateral prostatic biopsy showing infiltrating adenocarcinoma acinar, little differentiate and Gleason pattern 4+3, score 7/10. Patient notably had weight loss, nocturia, dysuria and a weak stream of urine since approximately the time of dapagliflozin/blinded therapy initiation. Tomography result 6 months after study drug initiated revealed a small solid lesion in the right upper lung lobe and a solid lesion in the right liver lobe. Liver biopsy results were compatible with well differentiated hepatocellular carcinoma. At the time of study enrollment, anti-HCV screen was negative, HBsAg was nonreactive and AST 37 IU/L (10-45), ALT 55 IU/L (6-48), Alk Phos 156 IU/L (45-145). Patient underwent a right hepatectomy plus segmentectomy I for cirrhotic liver CHILD-PUCH score A5 and hepatocellular carcinoma 15 months after study drug initiation.	121 211	family history colon cancer and unidentified cancer, smoker (40yr history), alcohol use (1 drink per day)	Receiving tx at time of report, goserelin acetate 3.6mg every 28 days for prostate cancer, right hepatecto my plus segmente ctomy for hepatocell ular carcinoma	Latency too short for grade 2 prostate CA, Hepatocellular carcinoma (HCC) diagnosed 3 months after stopping DAPA (only a 7 month latency for liver cancer). Risk factor for HCC is diabetes only. Negative family and personal history of autoimmune disorders. Positive family history of other cancers.	Yes, MB 102- 022, D1690C000 04, remains blinded	Unassessable /unclassifiable (due to blinding)
	Liver cancer	59	M	Diagnosed with life threatening liver cancer 6 weeks after initiating blinded study therapy with dapagliflozin/placebo. Patient received no treatment for the cancer and died 6 weeks later.	42		Death	Case was reported within another case, lacks information to adequately assess	yes, MB 102-033, remains blinded	Unassessable /unclassifiable
7143230 (1) 10/8/09	Chromaturia, Erythema, Hepatic Enzyme Increased, Liver Disorder, Mixed Liver Injury, Oedema, Purulent Discharge, Skin Ulcer	83	M	The patient experienced asymptomatic elevation of liver enzymes with an AST of 355 IU/L, ALT 419 IU/L, ALP of 355 IU/L with a normal total bilirubin 1.0 mg/dL and CK 68 U/L 173 days after initiating blinded dapagliflozin or placebo. Dapagliflozin/placebo, Pravastatin, and Niaspan therapies were discontinued in response to liver enzymes increase, 175 days after initiation of blinded dapagliflozin. At the time of event, patient was taking pravastatin for nine months, Niaspan for six months and just completed a course of levofloxacin antibiotic for a left lower leg ulcer 3 days earlier. Abdominal ultrasound revealed an echogenic liver parenchyma with borderline enlargement of the liver. Viral serology were negative for Hepatitis A IgM antibody, HBsAg screen and Hep B Core IgM antibody. Hepatitis C Virus Ab was < 0.2 (reference 0.0-0.9). HCV-PeR qualitative was negative and Anti-HAV (IgM), Hepatitis B Core IgM antibody and Anti-HCV were nonreactive. Liver function test (10 days post discontinuation) revealed a total bilirubin of 6.8 mg/dL, direct bilirubin 4.2 mg/dL (RR 0.0-0.3), AST 84 IU/L, ALT 126 IU/L, ALP 542 IU/L, gamma-glutamyl-transpeptidase (GGT) of 1256 IU/L (RR 11-42), total iron 63 mg/dL (RR 40-190), total iron-binding capacity (TIBC) 389 mcg/dL	173	levofloxacin, pravastatin, Niaspan	On-going at the time of report. Improvement in transaminases however total bilirubin increased to 6.8 mg/dl.	Levofloxacin or combination of three hepatotoxic medications. Six month latency when labs became abnormal, no history of alcohol use, negative hepatitis serologies	yes, blind broken but randomization not reported BMS double-blind study for patients with type II diabetes and moderate renal impairment who have inadequate glycemic control	Unassessable / Unclassifiable (due to blinding)

				(RR 250-425), prothrombin time (PT) 14.6 seconds (RR 10.0-13.0) and international normalized ratio (INR) 1.26 (RR 0.50-1.50). The patient's treatment was unblinded and all medications discontinued.						
7169806 (4) 11/6/09	Anaemia, Device Related Sepsis, Extremity Necrosis, General Physical Condition Abnormal, Hepatic Failure, Hepatic Steatosis, Hepatitis, Hepatitis Toxic, Inflammation, Jaundice, Liver Injury, Lung Consolidation, Malaise, Myopathy, Pneumonia, Polyneuropath y, Respiratory Failure, Septic Shock, Tracheobronc hitis, Urinary Tract Infection Enterococcal	68.08	F	The patient was hospitalized for treatment of bilateral pneumonia (confirmed by xray) 248 days after initiation of blinded dapagliflozin/glipizide/placebo treatment. The patient developed global respiratory insufficiency, despite noninvasive ventilation and ANTIBIOTIC therapy, and was intubated. She required artificial respiration for a total of 45 days. Laboratory results obtained 4 days after admission were CRP 204.7, AST 65, ALT 28, ALP 72, LDH 587, and GGT 58. Pneumogenic sepsis with septic shock requiring high doses of CATECHOLAMINES was diagnosed. Therapy with CEFOTAXIM and TOBRAMYCIN initially resulted in improvement and the CATECHOLAMINE dosage was reduced. Day 258 after study drug initiation laboratory results were CRP 27.7, AST 229, ALT 143, ALP 114, LDH 709 and GGT of 894. With intermittent pronounced. Approximately 10 days after discontinuation of study therapy and introduction of ANTIBIOTICS (AMPICILLIN + SULBACTAM, CLARITHROMYCIN, TOBRAMYCIN and CEFOTAXIME) for the treatment sepsis, the patient developed toxic hepatitis with cholestasis which continued to improve with the discontinuation of ANTIBIOTICS. The patient again experienced a fever and increased inflammatory parameters and was diagnosed with catheter associated sepsis by enterococcus faecium and urinary tract infection. After switching the ANTIBIOTIC therapy to VANCOMYCIN and GENTAMYCIN, the patient's general condition improved. As the infection and patient's general condition improved the ANTIBIOTIC was discontinued due to suspected hepatotoxicity. Respiratory insufficiency resolved, pneumonia resolved with sequel but patient continued to have intermittent icterus. A sonogram was negative for cholestasis. Cytomegalovirus (CMV) hepatitis was excluded. The patient was transferred from the hospital to a rehabilitation clinic for 30 days for a pronounced critical-illness polyneuropathy and myopathy. Once stabilized, a liver biopsy was performed and showed a "moderate chronic hepatitis probable nutritive or drug induced." Histology results from the liver biopsy revealed moderate chronic hepatitis (stage 3 according to Desmet with severe fibrosis/stage 3 according to Desmet). The impression was that this was atypical and most likely of nutritional or pharmaco-toxic origin with no signs of malignancy. No evidence of CMV hepatitis noted on examination under a light microscope. Less than a month after the liver biopsy the patient was hospitalized in a state of hepatic failure. It was reported the patient was admitted due to worsening of general condition and jaundice. Ascites puncture did not yield any signs of spontaneous bacterial peritonitis. On physical examination, the patient was somnolent and	248	pneumonia, clarithromycin, septic shock, obesity, dyslipidemia, diabetes mellitus 2	Death	Non-smoker, no alcohol use, but had slightly elevated transaminases at baseline prior to initiation of study drug that was attributed to obesity. Negative hepatitis serologies Patient died one year after initiation of blinded dapagliflozin treatment.	Yes, remains blinded	Unlikely, due to other disease processes and antibiotic therapy

disoriented. Chest x-ray revealed no signs of heart failure. Left basal consolidation was noted. Her ECG showed LT, sinus tachycardia, FQ 114/min and no repolarisation disturbances. She was treated with PREDNISOLONE therapy, with no improvement. Due to poor prognosis therapy was stopped and patient subsequently died.

CANAGLIFLOZIN CASES

Case # Version Rec'd Date	PTs	Age Yrs	Sex	Case Summary	Time to event onset (days)	Confounders	Outcome	Comments	Clinical Trial	Causality score WHO
9204449 (2) 4/2/13	Renal cell carcinoma	62	M	Subject experienced severe low back pain approximately 2.3 years after initiating blinded canagliflozin/placebo, was hospitalized, and computed tomography (CT) scan of abdomen showed a complex renal mass with extension into the perinephric compartment, diagnosed as left renal cell carcinoma. There was an enlarged lymph node noted in the left para aortic region below the left renal vein. Lytic lesion in the L3 vertebral body was consistent with a solitary metastatic deposit. Whole body bone scan results revealed a solitary bony metastasis involving L3, secondary to left renal tumor and no evidence of bony metastases elsewhere. CT scan of brain and chest showed no evidence of intracranial metastatic disease. A number of pulmonary nodules with 3 nodules measuring 4-6 mm were noted. A radical left nephrectomy was performed. Post-operative diagnosis was renal cell carcinoma, clear cell type with sarcomatoid and rhabdoid differentiation. Pathological stage: pT3a; tumor size was 100x82x60 mm; location was mid pole and nucleolar grade was 4. The renal vein was not involved, the tumor penetrated the renal capsule with involvement of perinephric fat; remainder of the kidney was unremarkable.	848	Obesity	Hospitalized	Diabetes, obesity, dyslipidemia, nonsmoker, uncircumcised, duration of treatment 1.5 years, bony mets and pulmonary nodules. Age is a risk factor. Advanced stage of cancer	yes, 28431754 DIA3008, Randomized to canagliflozin 100mg	Possible, time factor suggests an association, non-smoker
9264212 (3) 4/30/13	Adenocarcinoma of colon	64	M	The subject was hospitalized approximately 1006 days after initiating treatment with canagliflozin or placebo, underwent a colonoscopy and was subsequently diagnosed with obstructing adenocarcinoma of the colon with probable liver metastasis. One month prior to the event the subject developed abdominal pain and microcytic anemia. Study drug was discontinued 8 days prior to hospitalization. A palliative laparoscopic right hemicolectomy was performed (stage pT4aN3M1). A CT scan showed mesenterium peritoneal deposition and hepatogenous metastases. The pathologist concluded poorly differentiated adenocarcinoma (diameter 3.5 cm) of the right colon with invasion through all wall layers, through the serosa with perineural and vaso-invasive involvement, including the appendix. There were 13 of 22 lymph nodes with tumor localization. A peri-operative	998	Age, sex,	Hospitalized, hemicolectomy, not recovered	latency suggests drug related, missing info on smoking status, alcohol use, and GI history, no information on family history, age is risk factor	yes, 28431754 DIA3008, Randomized to canagliflozin 100mg	Conditional / unclassified, more data for proper assessment is needed

				inspection of the liver showed many metastases. No biopsy was performed. Due to the poor medical condition, the subject did not receive palliative chemotherapy.						
9300144 (1) 5/21/13	Metastatic carcinoma of the bladder	71.6	M	The subject underwent a vesico-prostatic ultrasound that showed vesical malignant neoplasm of moderate intensity 938 days after initiating blinded canagliflozin or placebo. The subject underwent a vesical transurethral resection where a 5-6 cm vesical tumor was removed 973 days after study drug was initiated and was discharged 2 days later. Treatment with blinded canagliflozin or placebo was interrupted for 3 days, then restarted. Pathology report of tumor showed nuclear positivity on 80% of neoplastic cells. Diagnosis was updated to metastatic bladder cancer upon the finding of hepatic metastases during surgery. Suspected cause was reported as bladder cancer. Study agent was stopped 1006 days after initiation. At the time of the report, the subject had not recovered from metastatic bladder cancer. The subject will start chemotherapy treatment. The investigator considered the event related was because it was not very common for the vesical tumor to metastasize in the liver. This case, involving the same subject is linked to 20100806571 and 20101105994.)	938	Ex-smoker, age, race (Caucasian)	Hospitalized, vesical transurethral resection, liver metastasis ongoing	51 yr history of smoking 2-3 packs per day, latency approx 2.5 year, no previous history or family history of cancer, uncircumsized, hepatic metastasis	yes, 28431754 DIA3008, unblinded canagliflozin 100mg	Possible due to smoking history
9307411 (2) 5/24/13	Transitional cell carcinoma of the bladder	79	M	Due to recurrent urinary tract infections, he was referred to a urologist by his general practitioner. An ultrasound of the renal tract was performed 790 days after initiating blinded canagliflozin/placebo, which revealed a 1.7 cm echogenic nodule in the bladder. A computed tomography (CT) scan was performed and showed the tumor visualized, but no further bladder or upper tract lesion identified. The subject experienced a urothelial carcinoma in situ, revealed via histology results. A bladder tumor was surgically removed and shown to be a transitional cell carcinoma in situ. Treatment with study agent was withdrawn on 826 days after initiation. The urologist had yet to discuss the information with the subject. At the time of the report, the subject had not recovered from urothelial carcinoma in situ and was uncertain if he wanted to remain in the study. The investigator considered the causality between urothelial carcinoma in situ and study agent as possible. The investigator commented that the subject had been on 2 years duration of therapy and renal tract tumors were noted in pre-clinical (rat) studies.	790	Recurrent UTIs, pipe smoker, age	Surgical resection of bladder tumor, treatment on-going at time of report	Recurrent UTIs, 2 year treatment duration, smoked a pipe for 6 years (may not be strong enough since 35 yrs old when he quit), no known history of chemical or radiation exposure.	yes, 28431754 DIA3008, unblinded canagliflozin 300mg	Possible, short history of pipe smoking, recurrent UTIs
9375571 (3) 6/28/13	Adenocarcinoma of colon, Bladder cancer, Gastrointestinal tract adenoma, Prostatomegaly	78	M	The subject was referred to a urologist 820 days after blinded canagliflozin/placebo due to hematuria and enlarged prostate. A computerized tomogram (CT) abdomen showed a 2.5 cm polypoid tumour arising from the dome of the bladder. No other urothelial or renal lesions were seen. Possible small polypoid lesion distal sigmoid colon and review with sigmoidoscopy was recommended. He underwent surgery for tumor removal 831 days after blinded canagliflozin initiation. Histology report showed high grade urothelial carcinoma invading	820	Smoker, age	Hospitalized, 2 surgeries, radiation and chemotherapy	ex-smoker (1 pack a day for 33 years, stopped at aged 50 years, adenocarcinoma of colon, latency of approx 2.25 years, had	yes, 28431754 DIA3008, unblinded canagliflozin 300mg	Possible for bladder cancer due to smoking history; Possible for adenocarcinoma of the colon

				<p>detrusor muscle. The subject was started on tamulosin for enlarged prostate. The subject was again hospitalized 873 days after study drug initiation for transurethral resection of the prostate (TURP) and removal of polyp from colon. Histology from specimens taken during surgery showed prostate with nodular hyperplasia with acute and chronic inflammation; sigmoid polyp: tubulovillous adenoma; rectosigmoid polyp: tubulovillous adenoma with high grade dysplasia, focal intramucosal adenocarcinoma (colon). The subject was to start course of chemotherapy and radiotherapy. The investigator updated the SAE terms to focal intramucosal adenocarcinoma of colon and tubulovillous adenoma (previously reported as colon polyps). The subject underwent radiation therapy to bladder for bladder tumor 922 days after study drug initiation. Outcome was reported as: radiation therapy to bladder, 64 gray in 32 fractions and chemotherapy regimen of mitomycin C 23 mg intravenous (IV) for one dose, and fluorouracil 4750 mg IV for 2 cycles.</p>				<p>polyps, no personal or family history of bladder cancer, no information on family history of polyps, circumcised. No exposure to dyes or chemicals nor any history of urinary tract infection (UTI), stones or bladder infections.</p>		
<p>9380720 (3) 7/2/13</p>	<p>Transitional cell carcinoma</p>	<p>64</p>	<p>M</p>	<p>The subject was diagnosed with T1 urothelial carcinoma with carcinoma in situ 945 days after initiation of blinded canagliflozin/placebo and underwent transurethral resection (TUR) bladder. Pathology result showed malignant, urothelial carcinoma (<i>nested variant</i>) with invasive growth in the lamina propria. The conclusion was carcinoma in situ (CIS) and T1 nested variant of the urothelial carcinoma, grade 3 of rare and aggressive clinical course and carcinoma in situ. A cystoscopy revealed urethra stricture (passable), in bladder papillary tissue and a protruding oslium on the right side and a small papillary tumor. Conclusion: dysfunctional micturation with overactive bladder. Treatment with study drug continued. Medical history included macroscopic hematuria approximately six years prior to study enrollment and computerized tomogram-urography performed revealed a dilated left ureter with a rather winding course (date of scan not reported). A rather irregular bladder was also visualized and a possible small concrement distally in the left ureter. Cystoureteroscopy revealed a paraostial diverticulum of the left ureteral ostium with bleeding from the left ureter. Ureterorenoscopy was performed on the left. Urine sample for cytology taken from the left ureter did not show clear evidence of malignancy. The small distal ureteral stone was removed. Retrograde ureterography and scope of the ureter did not reveal any anomaly of the collection system on the left. The bleeding appeared to be caused by the small ureteral stone. Urinary issues included waking up at night 6 times to urinate, weak flow and a sense of residue after urination. No urinary tract infection or hematuria. His urinalysis was negative. A computed tomography scan with intravenous pyelogram (CT-IVP) was to be scheduled to assess the upper urinary tract. Regarding the carcinoma, no muscle tissue</p>	<p>945</p>	<p>age</p>	<p>Hospitalized, transurethral resection (TUR) of bladder, on-going treatment for carcinoma in situ</p>	<p>non-smoker, circumcised, has not recovered at time of report</p>	<p>yes, 28431754 DIA3008, unblinded canagliflo zin 300mg</p>	<p>Possible, age is contributor y</p>

				invasion was noted. The reporter described the tumor as a rare aggressive clinical evolution despite the limited cell-atypia. Treatment with blinded canagliflozin/placebo was withdrawn 973 days after initiation. Re-TUR of the bladder performed 39 days after surgery showed no residual tumor and the presence of carcinoma in situ.						
9394850 (4) 7/11/13	Bladder transitional cell carcinoma	74	M	The subject experienced urinary bladder neoplasm 906 days after initiation of blinded canagliflozin/placebo therapy. Blinded study drug was withdrawn 825 days after initiation. An ultrasound and computed tomography (CT) confirmed presence of the neoplasm. The CT showed ventral wall of the urinary bladder affected, no lymphadenopathy, without extravesical extension. A transurethral resection of the tumor was performed 926 days after study drug initiation with no complications. The histology of the bladder neoplasm showed high grade urothelial papilocarcinoma. The size of the tumor was 10x30x25 mm. Oncology classification: pT1NOMx. Local chemotherapy with mitomycin C was initiated and therapy was ongoing.	906	current smoker	Hospitalization, surgery	smokes 30 cigarettes/day, high grade cancer, no family history of bladder cancer,	yes, 28431754 DIA3008, unblinded, canagliflozin 300mg	Possible, age and smoking status are contributors

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/s/

CHRISTINE E CHAMBERLAIN
10/03/2013

ALI NIAK
10/03/2013

STEVEN C JONES
10/03/2013

ALLEN D BRINKER
10/04/2013

MIN CHU CHEN
10/04/2013

Memorandum of Consultation

Division of Oncology Products 1 (DOP 1) Office of Hematology and Oncology Products (OHOP)

NDA #	202293
Request	Evaluation of an imbalance in the number of cases of bladder and breast neoplasms after initiating treatment with dapagliflozin
Product Proposed Indication	Dapagliflozin, 5 mg and 10 mg tablets Dapagliflozin (FORXIGA) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
NDA Sponsor	Bristol-Myers Squibb
Date of Consultation Consultation Requestor	08/22/2013 Abolade Adeolu Division of Metabolism and Endocrinology Products (DMEP) WO22 RM3239 Phone: 301-796-4264; Email: Abolade.Adeolu@fda.hhs.gov
Primary Reviewer Team Leader	Y Max Ning, MD, PhD V. Ellen Maher, MD
Date of Assignment Date Consult Completed	09/06/2013 09/22/2013

Consultation Request and Specific Questions

The original Request for this consultation from DMEP has the following background information and questions:

“Dapagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter 2 (SGLT2) being developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Dapagliflozin is a New Molecular Entity (NME), but not a first-in-class (i.e., canagliflozin, another SGLT2 inhibitor was approved on March 29, 2013). This Application is being reviewed for a second cycle under a six month review clock. During the first NDA review cycle, a Complete Response Letter was issued due to a benefit-risk assessment of modest efficacy with concerns of possible cancer risk, as well as

liver and cardiovascular safety. As reported by the Applicant and previously noted during the first review cycle, there is an imbalance in the number of cases of bladder and breast neoplasms after initiating treatment with dapagliflozin. The Application was the subject of a Dispute Resolution, at which time it was determined that a second Advisory Committee (AC) should be convened when the NDA is resubmitted. An AC is scheduled for early December 2013.

We would appreciate review and input from the Office of Hematology and Oncology Products on the following:

- 1) The significance of the observed imbalance in incidence of bladder and breast cancers in the pooled Phase 2b and 3 controlled clinical trials, and perspective on the expected background incidence of these malignancies*
- 2) The likelihood of the study drug contributing to the observed imbalance.*
- 3) Any additional advice or recommendations that OHOP has to offer.*

Because this NDA will be brought before an AC, we are requesting review within 30 days after receipt. We are attaching the following documents to aid your review: 1) The 30 month safety update (i.e., Dapagliflozin-30-Month-Update, refer to pages 52-78); 2) the Applicant's Response to Complete Response Letter (refer to pages 3-9); 3) Bladder Cancer Narratives; 4) Breast Cancer Narratives; 5) the Complete Response Letter (dated January 17, 2012) and 6) the Dispute Appeal — Denied Letter (dated September 14, 2012).

DOP1 Responses Regarding the Imbalance in Bladder Cancer Diagnosis

Response to Question 1: *The significance of the observed imbalance in incidence of bladder and breast cancers in the pooled Phase 2b and 3 controlled clinical trials, and perspective on the expected background incidence of these malignancies.*

Based on the verified data (see Appendix 1), the pooled 30-month updated safety analysis was from 21 randomized, controlled Phase 2b and 3 clinical trials of dapagliflozin. These trials enrolled approximately 10,000 patients in total and had an overall median treatment time of approximately one year. The pooled analysis revealed no overall imbalance in the diagnosis of malignancies between treatment arms during the trials. However, 9 cases (0.15%) of bladder cancer were diagnosed in 5936 patients on dapagliflozin compared to 1 case (0.03%) diagnosed in 3403 patients on control, suggestive of a considerable, cumulative imbalance in the diagnosis of bladder cancer during the trials. The incidence rate ratio associated with dapagliflozin versus control treatment was 5.2 for the tumor.

This difference in the cumulative incidence rate of bladder cancer during the clinical trials may be suggestive of an increased risk for bladder cancer diagnosis with dapagliflozin treatment. Close examination of the reported bladder cancer cases showed that all were diagnosed in men from 8 different countries. Approximately 60% of them used tobacco or had a history of using tobacco. Five of the 9 patients on dapagliflozin had their bladder cancer diagnosed between 1-2 years of treatment compared to none of patients not taking dapagliflozin during the same time period. The other 4 cases of bladder cancer in patients on dapagliflozin were detected within 6 months of study entry, compared to 1 case in patients on control. The following table summarizes key information about the bladder cancer cases diagnosed in the pooled analysis.

	Study ID (Country)	Age	Diagnosis Time in Trial (Day)	Tumor Type/Stage*/Grade	Tobacco Use	Prior Pioglitazone Use	Baseline Hematuria **
With Dapagliflozin	MB102014-34-524 (CND)	60	512	TCC/Ta/Low	25 PYs	No	Positive, Occult. (w/ureteric calculus)
	D1690C0000 4 -4916-2 (GMN)	76	727	TCC/T1/G3	20 PYs	No	Negative
	MB102030-90-880 (AGN)	67	144	TCC/T2/Mod	No	Yes	Positive: Trace
	D1690C0000 6 -1004-6 (AUS)	63	358	TCC/Ta/G2	100 PYs	No	Negative
	D1690C0000 6 -1501-6 (HUG)	67	399	TCC/ n/a /G2	No	No	Positive: Occult

	Study ID (Country)	Age	Diagnosis Time in Trial (Day)	Tumor Type/Stage*/ Grade	Tobacco Use	Prior Pioglitazone Use	Baseline Hematuria **
	D1690C0000 6 -2206-14 (USA)	66	581	TCC/ n/a /Low	53 PYs	No	Negative
	D1692C0000 5 -1-11 (JPN)	75	43	Papillary/T2/ G2	50 PYs	No	Positive, Occult
	D1690C0001 8 -7831-5 (USA)	48	74	TCC/ non- invasive/ Low	34 PYs	No	Negative
	D1690C0001 8 -7401-9 (CHN)	55	169	TCC/Non- invasive/ n/a	No	No	Positive: Trace
No Dapagliflozin	D1690C0001 9 -1016-7 (CND)	66	136	Papillary/micr o-invasive/ High	50 PYs	No	Positive: Occult
<p><i>TCC: Transitional Cell Carcinoma</i> <i>PYs: Pack Years</i> <i>n/a: not available</i> <i>* Localized disease per the report</i> <i>** Microscopic hematuria. Note that baseline hematuria was found in 8.5% of patients assigned to receive dapagliflozin and in 8.1% of patients assigned to receive control.</i></p>							

In the current NDA resubmission, there was one additional bladder cancer reported to the dapagliflozin arm of Study D1693C00005. This study was not included in the above pooled analysis due to uncompleted dataset lock at the time of analysis. This case (D1693C00005-6706-14) was a 53 year-old female who had TCC without muscle infiltration diagnosed 114 days after study treatment initiation. She used tobacco actively (40 PYs) but had no prior treatment with pioglitazone. Inclusion of this case along with the study in the pooled analysis resulted in a bladder cancer incidence rate of 0.17% (10/6045) for dapagliflozin-treated patients compared to a rate of 0.03% (1/3512) for patients not receiving dapagliflozin. The incidence rate ratio in the dapagliflozin-treated versus control-treated patients increased to 6.1.

According to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) statistics, the overall age-adjusted bladder cancer incidence rate during 2006-2010 was 20.7 per 100,000 men and women per year in United States. This rate corresponds to an annual incidence rate of 0.02%. The median age at diagnosis was 73 years. Given that the current pooled safety analysis was based on 21 trials conducted internationally, the SEER data may serve as a reference with regard to the expected background incidence of bladder cancer. Note that this 0.02% background

incidence rate of bladder cancer appears to be closer to the incidence rate of 0.03% observed in patient not taking dapagliflozin in the pooled analysis.

Taken together, the current available evidence appears to suggest an increased risk of bladder cancer diagnosis in patients taking dapagliflozin. Although determination of the attribution to dapagliflozin or of the causality could be difficult due to confounding factors, it is important to recognize that this increased bladder cancer risk was detected from the pooled analysis of 21 randomized, controlled trials that enrolled approximately 10,000 patients. In addition, the baseline hematuria rate (~8%) was balanced between the dapagliflozin and control arms, making the imbalanced bladder cancer diagnoses less likely secondary to potential detection bias. To the consultant's best understanding, this risk should not be disregarded because of the small number of patients diagnosed with bladder cancer in the trials, but rather should be further studied, carefully monitored, and possibly labeled as a Precaution or Warning for its safe use if approved.

Response to Question 2: The likelihood of the study drug contributing to the observed imbalance.

The non-clinical evidence provided by the applicant shows that dapagliflozin did not act as a carcinogenic agent in 2-year carcinogenicity studies or as a tumor growth enhancer in animal models bearing human transitional cell carcinoma (TCC). Please note that these animal models did not have TCC implanted in the bladder. The clinical relevance of findings from the studies remained unknown.

The current clinical data does not address whether dapagliflozin may promote or enhance TCC growth in long-term treatment. Given the observed increased risk of bladder cancer diagnosis in this large pooled analysis, the possibility that dapagliflozin or its metabolites may contribute to the increased incidence or diagnosis of bladder TCC could not be ruled out.

Response to Question 3: Any additional advice or recommendations that OHOP has to offer.

Regarding the increased risk of bladder cancer diagnosis associated with dapagliflozin, the consultant has the following suggestions for your consideration:

- A) Additional non-clinical assessments of whether dapagliflozin enhances or promotes TCC growth in animal models that closely simulate clinical use and elimination of dapagliflozin

-
- B) Analyses of products in the same class to investigate whether there is a class-effect on the risk of bladder cancer**
 - C) Seek advice from OSE and or the planned Advisory Committee meeting about dapagliflozin to determine whether additional studies are needed to better evaluate the bladder cancer risk associated with dapagliflozin**

Appendix 1: Distribution of bladder and breast cancers in the pooled safety analysis (verified by the applicant in September, 2013)

All Phase 2b and 3 Pool (Data cut used for 30-MU)													
Study ID	Total Number of Treated Patients	Number of Patients by Arm		Median Age (years) (range)*		Study Treatment Duration† (days) Median/Mean (range)*		Total Number of Malignancies in the Study‡		Number of Breast Cancers‡		Number of Bladder Cancers‡	
		Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)	Dapa (N)	Control (N)
MB102008	389	279	110	55.0-57.5	52-53	85/ 79.4-84.1	84-85/ 74.9-80.1	1	0	0	0	0	0
MB102009**	71	48	23	57.5-59	59	85/ 80.1-82.8	84/ 70.7	0	0	0	0	0	0
MB102013**	485	410	75	51-56	53	700-713/ 536.4-595.8	707/ 515.9	8	2	1	0	0	0
MB102014	546	409	137	53-56	54	708-712/ 574.4-599.3	701/ 541.1	7	3	1	0	1	0
MB102021	598	397	201	51-53	52	168/ 153.2-159.3	168/ 154.6	2	0	1	0	0	0
MB102022 (D1690C00004) ***	814	406	408	59	60	750.5/ 881.5	716.5/ 829.8	13	10	1	0	1	0
MB102028 (D1690C00005)	596	450	146	59-60	61	337/ 309-315.8	337/ 310	7	0	1	0	0	0
MB102029	252	168	84	66-68	67	720-721/ 528.5-558.0	700/ 479.3	2	2	0	0	0	0
MB102030	420	281	139	53-54.5	54	336-337/ 300.6-311.4	336/ 291.4	3	0	0	0	1	0
MB102032**	210	142	68	50.5-54.0	53.5	169/ 159.6-161.8	169/ 168.8	0	0	0	0	0	0
MB102033 (D1690C00006)	807	610	197	59-60	59	725-727/ 553.1-596.6	721/ 516.5	18	8	3	0	3	0
MB102034	638	430	208	51	54	168/ 154.2-155.4	168/ 155.9	0	2	0	0	0	0
MB102035	75	24	51	53.5	56-62	85.5/ 85	85-85.5/ 85-88.4	0	0	0	0	0	0
MB102045	44	23	21	59	54	87/ 87.9	85/ 83.4	0	0	0	0	0	0
MB102047 (D1690C00012)	182	91	91	62	61	714/ 612.1	714/ 642.1	2	2	1	0	0	0
MB102054	393	261	132	52-53	49.5	169/ 156.1-156.7	169/ 157.4	1	0	0	0	0	0
MB102061 (D1690C00010)	451	225	226	55	55	337/ 314.8	337/ 305.8	2	6	0	1	0	0
MB102064** (D1692C00005)	220	166	54	57-59	60	85/ 83.3-84.9	85/ 81.8	1	0	0	0	1	0
MB102067 (D1690C00018)	922	460	462	63	63	364/ 401.4	365/ 401.2	13	5	1	1	2	0
MB102080 (D1690C00019)	965	482	483	64	64	365/ 435.5	364/ 427	9	11	2	1	0	1
MB102106 (D1692C00006)	261	174	87	58-61	62	168/ 157.3-161.5	168/ 158.8	0	0	0	0	0	0
Total (All Phase 2b/3 Pool)	9339	5936	3403	58	59	336/384.4	337/390.4	89	51	12	3	9	1

Abbreviations: Dapa, dapagliflozin.

* Median or range of medians across treatment arms;

† Extent of Exposure to Study Medication - Double-blind Period;

‡ Total number of subjects in the study with at least one event

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/s/

YANGMIN NING
10/02/2013

VIRGINIA E MAHER
10/03/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **December 20, 2011**

To: Mary Parks, MD, Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review of Patient Labeling (Medication Guide)

Drug Name (established name): (dapagliflozin propanediol)

Dosage Form and Route: Tablet

Application Type/Number: 202293

Applicant: Bristol-Myers Squibb

OSE RCM #: 2011-82

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for dapagliflozin propanediol.

On December 27, 2010, Bristol-Myers Squibb submitted a new drug application for dapagliflozin propanediol tablets for the treatment of type 2 diabetes in adults as an adjunct to diet and exercise to improve glycemic control. A TRADENAME has not yet been designated for dapagliflozin propanediol tablets. Therefore, we have used TRADENAME throughout the DMPP review of the MG.

2 MATERIAL REVIEWED

- Draft dapagliflozin propanediol Medication Guide received on December 27, 2010 and received by DMPP on December 9, 2011
- Draft dapagliflozin propanediol Prescribing Information (PI) received on December 27, 2010, revised by the Review Division throughout the current review cycle and received by DMPP on December 9, 2011

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON W WILLIAMS
12/20/2011

MELISSA I HULETT
12/20/2011

LASHAWN M GRIFFITHS
12/20/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 9, 2011

Reviewer(s): Lissa C. Owens, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos M Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s) & Strength: Forxiga (Dapagliflozin) Tablets
5 mg and 10 mg

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol-Myers Squibb

OSE RCM #: 2011-241

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container labels and the carton labeling submitted on December 28, 2010 for Forxiga (Dapagliflozin) Tablets, 5 mg and 10 mg, for areas of vulnerability that can lead to medication errors in response to a request from the Division of Metabolism and Endocrinology Products.

1.1 PRODUCT INFORMATION

Forxiga (Dapagliflozin) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The usual recommended dose is one 10 mg tablet taken by mouth once daily. Forxiga will be available as a yellow 5 mg round tablet with “5” engraved on one side and “1427” engraved on the other side and a yellow 10 mg diamond-shaped tablet with “10” engraved on one side and “1428” engraved on the other side. This product will be packaged in bottles containing 30, 90, or 500 tablets, 7 count blister cards for physician’s samples and boxes containing 10 X 10 count blister cards for hospital unit dose use. (b) (4)

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 27, 2010
- Carton Labeling submitted December 27, 2010

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors. We recommend the following:

A. GENERAL COMMENTS (ALL CONTAINER LABELS AND CARTON LABELING)

1. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXXX-x). Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.
2. The established name should be revised (b) (4) to ‘(Dapagliflozin)’. The dosage strength of this product is based on the active moiety (b) (4).
3. Remove (b) (4) on the label.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. HOSPITAL UNIT DOSE BLISTERS

10 count Blister Label

1. Revise the presentation of the strength statement to the same color scheme as in the container labels to better differentiate the strengths (5 mg (b)(4) and 10 mg (b)(4)).

Carton Labeling

1. Revise the strength statement to read “XX mg per tablet” or “XX mg/tablet”.

C. PHYSICIAN SAMPLES

7 count Blister Label

1. Revise the strength statement to read “XX mg per tablet” or “XX mg/tablet”.
2. Increase the prominence of the statement ‘Push tablet through from the other side’.
3. Revise the color block used to highlight the strength statement to the same color scheme as in the container labels to better differentiate the strengths (5 mg (b)(4) and 10 mg (b)(4)).

Carton Labeling

1. Revise the strength statement to read “XX mg per tablet” or “XX mg/tablet”.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARLOS M MENA-GRILLASCA on behalf of LISSA C OWENS
12/09/2011

CARLOS M MENA-GRILLASCA
12/09/2011

CAROL A HOLQUIST
12/12/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202293

Name of Drug: Dapagliflozin tablets

Applicant: Bristol-Myers Squibb Company (in collaboration with AstraZeneca Pharmaceuticals)

Labeling Reviewed

Submission Date: NDA 202293 for dapagliflozin was submitted on December 27, 2010, (received on December 28, 2010), and contained labeling in SPL format. Revised labeling was submitted on November 8, 2011, in response to comments from the Division, but did not contain labeling in SPL format. Therefore, the Word version submitted on November 8, 2011 was used for this review.

Background and Summary Description

This NDA is for dapagliflozin tablets, a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is a first-in-class new molecular entity. The recommended dose is 10 mg taken once daily at anytime of the day regardless of meals. Dosage form and strengths is 10 mg and 5 mg tablets.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement and described in italic blue font.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant, along with other labeling comments identified by the review team, by December 9, 2011. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies, and the resubmitted labeling will be used for further labeling discussions.

Mehreen Hai, Ph.D.	December 2, 2011
Regulatory Project Manager	Date
Julie Marchick, M.P.H.	December 5, 2011
Acting Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and

Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval. *Note: The “issued” date located at the end of the full prescribing information is redundant and should be removed.*

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Note: The word “clinical” has been omitted.

For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

This section is required and cannot be omitted.

Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

MEHREEN HAI
12/06/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 29, 2011

To: Mary H. Parks, MD
Director, Division of Metabolism and Endocrinology Products
Office of New Drugs

Through: Solomon Iyasu, MD, MPH
Director, Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Diane K. Wysowski, PhD, MPH
Team Leader, Division of Epidemiology I

From: Christian Hampp, PhD
Visiting Associate/Epidemiologist,
Division of Epidemiology I

Subject: Updated Analysis of Bladder Cancer and Breast Cancer with
Dapagliflozin

Drug Name(s): Dapagliflozin

Submission Number: n/a

Application Type/Number: IND 068652
NDA 202293

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1476

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EXECUTIVE SUMMARY

My previous reviews, dated June 7, 2011, and July 20, 2011, provided rates of bladder cancer among patients enrolled in the dapagliflozin (Bristol-Myers Squibb and AstraZeneca, NDA 202293) phase 2b and 3 clinical trials program, including studies with placebo and active controls. Since then, the sponsors have provided their July 15, 2011, Integrated Safety Database with additional follow-up data. Since the breast cancer review conducted by Jing (Julia) Ju, PharmD, PhD, Division of Epidemiology I (DEPI-I), three additional cases of breast cancer have been detected, one exposed to dapagliflozin, two exposed to placebo. Among the latter, one case was diagnosed as ductal carcinoma *in situ*. This review updates previous DEPI-I reviews on bladder cancer and breast cancer in the clinical trials of dapagliflozin.

Using the most recent data, I replicated the sponsors' calculations of bladder and breast cancer rates in their clinical trial program. In addition, data from the Surveillance, Epidemiology, and End Results (SEER) database were used as external comparators to calculate standardized incidence ratios (SIR). Separate calculations for breast cancer were conducted with and without the ductal carcinoma *in situ* case.

With nine cases of bladder cancer in male patients exposed to dapagliflozin and one case among male controls, the adjusted rate ratio of the incidence of bladder cancer was 5.38 (95% CI, 0.84 – 122.2), $p=0.185$. Compared with an age-matched male U.S. diabetic population, the SIR of observed versus expected cases in males exposed to dapagliflozin was 2.80 (95% CI, 1.36 – 5.13), $p=0.008$. Two cases of bladder cancer would be expected among controls, where only one case was observed.

Ten cases of breast cancer occurred in the female dapagliflozin-exposed clinical trial population, and three cases occurred among controls, with one control patient diagnosed with ductal carcinoma *in situ*. Including this case, the adjusted rate ratio was 1.90 (95% CI, 0.52 – 8.93), $p=0.374$, and excluding this case, 2.76 (95% CI, 0.64 – 19.21), $p=0.242$. Observed case counts in dapagliflozin-exposed subjects were similar to expected case counts based on SEER; however, observed counts among controls were lower than expected. When the *in situ* case was included, six cases of breast cancer were expected among controls and only three were observed. When the *in situ* case was excluded, five cases of breast cancer were expected and only two were observed. Although these small numbers could be due to random variation, one should not discard the possibility that the clinical trials sample was at lower risk at baseline, when compared to the general U.S. diabetic population. This possibility would be consistent with a harmful drug effect in the exposed, resulting in as-expected counts.

To summarize, the clinical trials were not powered to detect differences in bladder or breast cancer rates between patients exposed to dapagliflozin and patients exposed to the control substance. Despite the lack of statistical significance, rate ratios especially for bladder cancer are concerning and this potential risk should be viewed in light of the expected drug benefits. In the case of approval, the risks for both bladder and breast cancer deserve continued attention, and the sponsors have proposed pharmacoepidemiologic studies to investigate these risks. The respective study protocols are subject to separate DEPI-I reviews.

1 BACKGROUND/HISTORY

My previous reviews (Hampp C., Incidence of Bladder Cancer in a Diabetic Population, June 7, 2011, and Hampp C., Updated Analysis - Incidence of Bladder Cancer in a Diabetic Population, July 20, 2011, both available in DARRTS) provided incidence rates and incidence rate ratios of bladder cancer among patients enrolled in the dapagliflozin (Bristol-Myers Squibb and AstraZeneca, NDA 202293) phase 2b and 3 clinical trials program, including studies with placebo and active controls. Since then, the sponsors have provided their July 15, 2011, Integrated Safety Database with additional follow-up data. Three new bladder cancer cases that occurred since the previous version of the Integrated Safety Database were already included in my previous reviews, but additional follow-up data necessitated the recalculation of the incidence estimates.

Since the breast cancer review conducted by Jing (Julia) Ju, PharmD, PhD, Division of Epidemiology I (DEPI-I), three additional cases of breast cancer have been detected, one exposed to dapagliflozin, two exposed to placebo. Among the latter, one case was diagnosed as ductal carcinoma *in situ*.

This review updates previous DEPI-I reviews on bladder cancer and breast cancer in the clinical trials of dapagliflozin.

2 REVIEW METHODS AND MATERIALS

Upon request, the sponsors provided trial-specific counts and follow-up durations for bladder cancer and breast cancer, separate for males and females, from the July 15, 2011 Integrated Safety Database. These data were analyzed and results were compared with the sponsors' own calculations provided in response to our request from August 15, 2011. Consistent with the sponsors' approach, rate ratios were calculated including only studies where at least one cancer of interest occurred, and rate differences included all studies. For rate ratios, the conditional maximum likelihood estimate was used. In this review, the Cochrane-Mantel-Haenszel formula was used for the calculation of rate differences in, which was compared with the sponsor's approach based on a paper by Tian et al. (1). Because one of the new cases of breast cancer in a patient exposed to placebo was categorized as ductal carcinoma *in situ*, which is typically not considered breast cancer because of low potential for invasion and spread, this review includes separate analyses based on the inclusion and exclusion of this case.

Incidence rates for both bladder and breast cancer were also compared with background rates in the general U.S. population. For this review, age- and sex-specific incidence rates were extracted from the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute (2). These rates were adjusted with a literature-based factor to reflect the increased risk for bladder and breast cancer in a diabetic population. As described in greater detail before (Hampp C., Incidence of Bladder Cancer in a Diabetic Population, June 7, 2011), the hazard ratios for bladder and breast cancer associated with diabetes were derived from studies that compared diabetic populations to non-diabetics. Therefore, these hazard ratios were adjusted to reflect that SEER data include diabetic patients, with the assumption that their proportion is the same as in the U.S. general population older than 20 years of age (11.3%, American Diabetes

Association (3)). For this review, a downward-adjusted hazard ratio of 1.40 was calculated for bladder cancer (4). Based on a meta-analysis by Larsson et al. (5), a hazard ratio of 1.18, downward-adjusted from 1.20, was calculated for breast cancer.

Because all cases of bladder cancer were reported in males, observed counts of bladder cancer in the dapagliflozin clinical trial program were compared with expected case counts in an age-matched male diabetic background population. Similarly, case counts of breast cancer were compared with expected case counts in an age-matched female diabetic background population. SEER provides separate incidence estimates for breast cancer and for breast cancer *in situ*. The sum of both incidence rates was used when the one breast cancer *in situ* case was included and only the rate for breast cancer was used when the *in situ* case was excluded.

3 RESULTS OF REVIEW

3.1 BLADDER CANCER

3.1.1 Clinical Trials

In the July 15, 2011, Integrated Safety Database, ten subjects were reported with a diagnosis of bladder cancer in the Phase 2b and 3 clinical trials on dapagliflozin. Nine of these cases occurred in the active treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76. Total follow-up of male patients randomized to dapagliflozin was 3165.8 subject-years (Table 1) after cases were censored at the date of their case diagnosis. With nine cases of bladder cancer occurring in male subjects exposed to dapagliflozin during this time, the crude incidence rate amounted to 284.3 (95% CI, 129.7 – 539.7) new cases per 100,000 subject-years. This compares to one case during 1854.4 subject-years in controls, or 53.9 (95% CI, 0.7 – 300.0) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of bladder cancer between active treatment and controls was in agreement with the sponsors' calculation: 5.38 (95% CI, 0.84 – 122.2), with a two-sided *p*-value of 0.185. The sponsors calculated the adjusted rate difference as 209 cases per 100,000 patient-years (95% CI, -305 – 688). (Note: the lower bound of this wide confidence interval is negative 305, thus including the possibility of no difference or even a protective drug effect.) The Mantel-Haenszel calculation conducted for this review yielded a rate difference of 237 cases per 100,000 patient-years (95% CI, 20.3 – 455) with a confidence interval excluding the null, *p*=0.03.

3.1.2 SEER Data

Based on SEER data, slightly more than three cases (3.22) of bladder cancer would be expected in the male dapagliflozin population (Table 1) at a crude rate of 101.4 new cases per 100,000 subject years. The SIR of observed (n=9) versus expected cases (n=3.22) in males exposed to dapagliflozin was 2.80 (95% CI, 1.36 – 5.13), *p*=0.008. Two cases (2.08) would be expected among controls, where only one case was observed.

Table 1. Expected cases of bladder cancer in the male clinical trial sample

Age at diagnosis	Males			
	Observed cases, dapagliflozin	Dapagliflozin, person-time, males	Projected incidence, diabetic population, based on SEER data*	Expected bladder cancer cases in dapagliflozin patients
<25	0	1.52	0.4	0.0000
25-29	0	16.83	0.7	0.0001
30-34	0	47.98	1.5	0.0007
35-39	0	92.12	3.2	0.0029
40-44	0	183.27	7.0	0.0129
45-49	1	325.83	15.6	0.0509
50-54	0	450.45	31.8	0.1433
55-59	1	638.84	63.8	0.4077
60-64	2	591.6	111.8	0.6612
65-69	3	468.37	183.1	0.8578
70-74	2	241.81	275.3	0.6656
75-79	0	87.41	372.5	0.3256
80-84	0	19.3	455.5	0.0879
85+	0	0.46	506.9	0.0023
sum	9	3165.8	--	3.22

*per 100,000 person-years

3.2 BREAST CANCER

3.2.1 Clinical Trials

3.2.1.1 Including Breast Cancer *In Situ*

In the July 15, 2011, Integrated Safety Database, 13 subjects were reported with a diagnosis of breast cancer in the Phase 2b and 3 clinical trials of dapagliflozin, including one case of ductal carcinoma *in situ*. Ten of these cases occurred in the active treatment arms and three in placebo arms. All of these diagnoses were made in female subjects between the ages of 53 and 74. Total follow-up of female patients randomized to dapagliflozin was 2701.6 subject-years (Table 2) after cases were censored at the date of their case diagnosis. With ten cases of breast cancer occurring in female subjects exposed to dapagliflozin during this time, the crude incidence rate amounted to 370.2 (95% CI, 177.2 – 680.8) new cases per 100,000 subject-years. This compares to three cases during 1361.6 subject-years in controls, or 220.3 (95% CI, 44.3 – 643.7) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of breast cancer between active treatment and controls was 1.90 (95% CI, 0.52 – 8.93), with a two-sided *p*-value of 0.374. The sponsors calculated the adjusted rate difference as 228 cases per 100,000 patient-years (95% CI, -537 – 806), with the confidence interval

including the possibility of no difference. The Mantel-Haenszel calculation conducted for this review yielded a rate difference of 189 cases per 100,000 patient-years (95% CI, -128 – 506), with a confidence interval also including the null, $p=0.244$.

3.2.1.2 Excluding Breast Cancer *In Situ*

The following sensitivity analysis was not performed by the sponsors. After exclusion of the *in situ* case, only two cases of breast cancer occurred among controls during 1361.6 subject-years of follow-up, or 146.9 (95% CI, 16.5 – 530.3) new cases in controls per 100,000 subject-years. The adjusted rate ratio comparing the incidence of breast cancer between active treatment and controls was 2.76 (95% CI, 0.64 – 19.21), with a two-sided p -value of 0.242. The Mantel-Haenszel calculation conducted for this review yielded a rate difference of 248 cases per 100,000 patient-years (95% CI, -46.5 – 543), with a confidence interval including the null, $p=0.099$.

3.2.2 SEER Data

3.2.2.1 Including Breast Cancer *In Situ*

Based on SEER data, I calculated that almost 12 cases (11.85) of breast cancer including *in situ* would be expected in the female dapagliflozin population (Table 2) at a crude rate of 438.6 new cases per 100,000 subject-years. The SIR of observed ($n=10$) versus expected cases ($n=11.85$) in females exposed to dapagliflozin was 0.84 (95% CI, 0.43 – 1.50), $p=0.62$. Six cases (6.14) would be expected among controls, where only three cases were observed, including one *in situ* case.

Table 2. Expected cases of breast cancer including *in situ* in the female clinical trial sample

Age at diagnosis	Females			
	Observed cases, dapagliflozin	Dapagliflozin, person-time, females	Projected incidence, diabetic population, based on SEER data*	Expected breast cancer cases in dapagliflozin patients
<25	0	5.64	2.0	0.0001
25-29	0	14.92	10.3	0.0015
30-34	0	33.69	33.8	0.0114
35-39	0	64.31	83.0	0.0534
40-44	0	143.65	184.9	0.2656
45-49	0	260.02	290.5	0.7554
50-54	1	438.49	358.1	1.5703
55-59	2	586.23	441.3	2.5873
60-64	5	553.3	532.1	2.9442
65-69	1	309.63	602.2	1.8646

70-74	1	206.67	612.4	1.2657
75-79	0	75.26	636.1	0.4787
80-84	0	8.36	589.4	0.0493
85+	0	1.4	465.1	0.0065
sum	10	2701.6	--	11.85

*per 100,000 person-years

3.2.2.2 Excluding Breast Cancer *In Situ*

Based on SEER data, more than nine cases (9.44) of breast cancer would be expected in the female dapagliflozin population (Table 3) at a crude rate of 349.4 new cases per 100,000 subject-years. The SIR of observed (n=10) versus expected cases (n=9.44) in females exposed to dapagliflozin was 1.06 (95% CI, 0.54 – 1.89), p=0.82. Five cases (4.90) would be expected among controls, where only two cases were observed.

Table 3. Expected cases of breast cancer not including *in situ* in the female clinical trial sample

Age at diagnosis	Females			
	Observed cases, dapagliflozin	Dapagliflozin, person-time, females	Projected incidence, diabetic population, based on SEER data*	Expected breast cancer cases in dapagliflozin patients
<25	0	5.64	1.8	0.0001
25-29	0	14.92	9.4	0.0014
30-34	0	33.69	30.7	0.0104
35-39	0	64.31	70.8	0.0455
40-44	0	143.65	142.5	0.2047
45-49	0	260.02	222.6	0.5789
50-54	1	438.49	275.9	1.2100
55-59	2	586.23	348.1	2.0405
60-64	5	553.3	426.7	2.3609
65-69	1	309.63	485.7	1.5040
70-74	1	206.67	502.4	1.0383
75-79	0	75.26	531.9	0.4003
80-84	0	8.36	508.8	0.0425
85+	0	1.4	424.2	0.0059
sum	10	2701.6	--	9.44

*per 100,000 person-years

4 SUMMARY AND RECOMMENDATIONS

This review updates my previous analyses with additional follow-up information and newly includes an analysis of breast cancer.

Bladder cancer

Because no new cases of bladder cancer were added and total follow-up time was increased by only about 5%, results for bladder cancer changed little compared to the previous reviews. This update found an adjusted rate ratio of 5.38, $p=0.185$, rate differences of 209 (not significant, sponsors' calculations) and 237 (stat. significant, this review) additional cases per 100,000 patient-years, and a SIR of observed versus expected cases among dapagliflozin-exposed subjects of 2.98, $p=0.008$.

The comparison of results from analyses performed by the sponsors with results from this review deserves comment. While the calculations of rate ratios are in agreement with the sponsors' results, the approaches to calculate risk differences and the resulting estimates differ. The sponsors' approach (1) is generally considered conservative and leads to wider confidence intervals and thus, the possibility of missing a true signal. At the time of this draft, we were unsuccessful in replicating the sponsors' risk difference calculations using the same approach. The Mantel-Haenszel approach used in this review produces narrower confidence intervals, but its applicability may be limited because small case counts may not support the normal approximation used in the Mantel-Haenszel test. In the bladder cancer analysis, this would lead to different conclusions, since only the Mantel-Haenszel approach resulted in a statistically significant rate difference between dapagliflozin and control. Nevertheless, since the rate ratio estimate was not statistically significant, the statistical significance of the Mantel-Haenszel risk difference should not be viewed as decisive.

Although the clinical trials were not powered to examine cancer as an adverse event and statistical significance was not reached in the clinical trials, a rate ratio of 5.38 for an important outcome such as bladder cancer is a cause for concern.

Breast cancer

An important factor in the interpretation of breast cancer risk associated with dapagliflozin is the consideration of the single *in situ* case that occurred in a control subject. Breast cancer *in situ* is considered to have a low potential for invasion and spread, so including it with invasive breast cancer is controversial. Although neither inclusion nor exclusion of this case affected statistical significance, the incidence rate ratio for breast cancer increased from 1.90 (95% CI, 0.52 – 8.93) with the *in situ* case to 2.76 (95% CI, 0.64 – 19.21) without the *in situ* case for dapagliflozin-exposed subjects compared to controls. The rate difference changed from 189 to 248 additional cases per 100,000 patient-years, after the exclusion of the *in situ* case.

The observed case counts in dapagliflozin-exposed subjects were similar to the expected case counts; however, observed counts among controls were lower than expected. When the *in situ* case was included, six cases of breast cancer would be expected and only three were observed. When the *in situ* case was excluded, five cases

of breast cancer would be expected and only two were observed. Although these small numbers could be due to random variation, one cannot exclude the possibility that the clinical trials population was at lower risk at baseline, either due to careful selection based on study criteria, or to lower breast cancer rates outside of the U.S. where most study subjects were recruited. If the entire study sample was at lower risk than the population control, apparently similar breast cancer rates between the dapagliflozin-exposed clinical trial sample and the general U.S. population could indicate an increased risk associated with dapagliflozin.

Findings of this review should be viewed in the light of several limitations. Cancer rates in SEER reflect the U.S. general population, while most of the clinical trial subjects were enrolled outside of the U.S., and international studies on the epidemiology of bladder cancer and breast cancer often found lower rates compared to the U.S. Also, clinical trial populations are often highly pre-screened for certain co-morbidities, which may result in an underestimated cancer incidence rate when clinical trial subjects are compared with the general population. On the other hand, increased surveillance in a clinical trial setting, together with urinary symptoms associated with dapagliflozin could increase case detection of bladder cancer and lead to higher estimates compared to the background population. However, this would not apply to breast cancer. Lastly, it should be considered that the literature-based factors to adjust SEER estimates for a diabetic population are subject to uncertainty regarding their validity.

To summarize, the clinical trials were not powered to detect differences in bladder or breast cancer rates between patients exposed to dapagliflozin and patients exposed to the control agent. Using SEER data, bladder cancer event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Breast cancer events occurred at a lower than expected rate in women randomized to control substances, with a possible explanation of a healthier sample in the trials. In contrast to lower rates among controls, observed rates among dapagliflozin-exposed females matched expected rates, which could indicate a harmful drug effect. However, limitations suggest that comparisons between clinical trial data and a reference population should be carefully interpreted.

Rate ratios especially for bladder cancer are concerning and this potential risk should be viewed in light of the expected drug benefits. If dapagliflozin is approved, the risks for both bladder and breast cancer deserve continued attention, and the sponsors have proposed pharmacoepidemiologic studies to investigate these risks. The respective study protocols are subject to separate DEPI-I reviews.

Christian Hampp, PhD

cc: EganA/ParksM/DunnS/IronyI/BishaiJ/HaiM/DMEP
HamppC/JuJ/WysowskiD/IyasuS/TossaM/OSE

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/s/

CHRISTIAN HAMPP
11/29/2011

SOLOMON IYASU
11/29/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 23, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Solomon Iyasu, MD, MPH, Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER
Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: (b) (4)


Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-1273

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11/23/2011

SOLOMON IYASU
11/23/2011



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From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
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Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: (b) (4)

Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-3281

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11/23/2011

SOLOMON IYASU
11/23/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1**

Date: 21 November 2011

To: Mary Parks, M.D., Director,
Division of Metabolic and Endocrine Products (DMEP)

Reviewer: Leonard Seeff, MD, Hepatologist
Office of Surveillance and Epidemiology (OSE)

Through: Allen Brinker, MD, MS, Medical Team Leader
Division of Pharmacovigilance 1 (DPV1)

Drug Name: dapagliflozin

NDA Number: 202-293

Applicant/sponsor: BMS & AstraZeneca

OSE RCM #: 2011-3775

Issue: Review of cases of liver injury in the clinical development
program for dapagliflozin.

INTRODUCTION

In a consult request dated 5 October 2011, DMEP asked OSE to review a single case of serious liver injury possibly associated with the registrational agent, dapagliflozin. This case is an addition to a review¹ of 8 other similar cases performed earlier in preparation for the FDA Advisory Committee meeting for dapagliflozin.

In an initial review of the case (D1690C00018-201-8), it appeared that reaching a diagnosis was compromised by missing information, so that DMEP was requested to collect the additional relevant data. While awaiting this information, the dapagliflozin sponsor submitted an addendum to the initial Hepatic Adjudication Report that included a total of 7 cases (4 with known receipt of dapagliflozin; 3 blinded to treatment allocation) that met the criteria for evaluation by the Hepatic Adjudication Committee (HAC). The cases and treat allocation are listed below in the table.

Patient ID	Treatment
MB102029-4-276	Dapagliflozin
MB102054-24-498	Blinded
MB102077-88-70220	Blinded
D1690C00010-1003-24	Dapagliflozin—no narrative
D1690C00019-5719-6	Dapagliflozin
D1691C00003-3306-11	Blinded
D1690C00018-201-8	Dapagliflozin

BACKGROUND

In review, dapagliflozin is an inhibitor of SGLT2 (sodium glucose co-transporter 2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin results in the direct, and insulin-independent, elimination of glucose by the kidney. The sponsor plans to market two doses, 5 mg (for patients at risk for volume depletion due to diuresis) and 10 mg (standard dose). Dapagliflozin, if approved, will be first-in-class for the treatment of Type 2 diabetes.

¹ Memorandum dated 21 June 2011. Leonard Seeff to Mary Parks. Review of cases of serious liver toxicity arising in NDA 202293 (dapagliflozin).

MATERIALS AND METHODS

Case narratives and other information were reviewed from materials provided to OSE from DMEP. These materials were limited to:

- Case narratives
- Hepatic ADJUDICATION REPORT (ADDENDUM – dated 25 October 2011).

As conducted in the previous OSE review¹, the 7 cases included in this document were subjected to an assessment of causality for liver injury based on a grading system developed by the NIH Drug-Induced Liver Injury Network (DILIN) Study group.² This grading system has been applied by DILIN to perform causality assessment of cases of liver injury that have occurred in patients in a clinical practice setting treated with marketed drugs who were then referred to the DILIN network for evaluation. The grading of causal association with a particular drug is as follows:

- Definite = >95% likelihood
- Highly Likely = 75% to 94% likelihood
- Probable = 50% to 74%
- Possible = 25% to 49%
- Unlikely = <25%
- Insufficient information to classify

REVIEW OF CASES

MB102029-4-276 (Dapa). The patient, an 83 year old white male with type 2 diabetes and several of its complications, started treatment with dapagliflozin that continued for 175 days when it was discontinued because of observed liver-related biochemical abnormalities on that day (ALT 444, AST 320, ALP 410, total bilirubin 1.3) as well as two days earlier (ALT 419, AST 355, ALP 355, total bilirubin 1.0). Prior to that time, starting from the initiation of treatment with dapa, his liver chemistries had been quite normal. He did have a transient episode of hypotension on day 14 of therapy but no liver chemistries are shown for that time. He had been on treatment with lisinopril and hydrochlorothiazide that were discontinued when the hypotensive episode occurred. Other drugs he was receiving at this early time included various forms of insulin, and at differing time intervals, pravastatin, acetylsalicylic acid, iron, cyanocobalamin, gabapentin, niacin, cephalexine, and levofloxacin. Niacin had been started 2 days prior to the first set of identified abnormalities and was stopped 4 days later.

² Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009; 32 (1):55-68.

In follow-up 3 weeks after day 175, there was a dramatic decline in his serum aminotransferase levels, but an increase in his ALP level (445 increasing to 601) and particularly his bilirubin value that reached a peak of 8.9 mg/dL. Over the course of the following 150 days, his aminotransferase values began to slowly drift down whereas his ALP level increased somewhat, while his serum bilirubin value remained abnormal but decreasing slowly so that by day 372 (200 days after the first identified abnormalities), all values had returned to normal.

He apparently had no relevant symptoms when the abnormalities were noted. Tests for hepatitis A, B and C were all negative. An ultrasound showed slight hepatomegaly but a later MRI revealed intrahepatic duct dilatation which prompted an ERCP showing a stricture at the bifurcation of the left and right ducts suggestive of a Klatskin cholangiocarcinoma. Cytology brushings, however, were negative for malignancy. A stent was placed. He was then found to have a urinary tract infection and urosepsis that was treated with antibiotics.

Cardiac work-up revealed a low ejection fraction and later congestive heart failure as a consequence of a myocardial infarction for which he received appropriate therapy. Continued efforts to prove the existence of cholangiocarcinoma that included several PET scans were unfruitful but he did have elevated levels of CA-19.9 and CEA. With continued treatment, his cardiac disease and urosepsis resolved. He had occasional increases in serum enzyme values, especially the AST, ALP, and a single elevation in his serum bilirubin. He continues to be followed.

Comment: This is clearly not an instance of hepatotoxicity. The abnormalities occurred quite late after starting dapa (about 6 months) and the pattern was largely that of a cholestatic form of liver injury. Imaging studies and an ERCP indicated that there was intraductal pathology that appeared responsible for jaundice that was relieved by a stent. The precise basis for the identified stricture is unclear but is likely to be that of a cholangiocarcinoma. [Classification = Unlikely.]

MB102054-24-498 (Treatment Blind). The patient is a 63 year old Chinese male with type 2 diabetes, hypertension, a previous arrhythmia (resolved since 2007), past cholecystitis, and benign prostatic hypertrophy, treated in the study with a drug blinded as to type. Concurrent therapies included: hydrochlorothiazide, dihydralazine, reserpine, and chlordaizepoxide. All liver chemistries were normal at baseline and for the first two weeks; also negative at baseline were the hepatitis B and C serologies. On day 26, the patient developed an upper respiratory tract infection. The patient self-treated himself with over-the-counter medication containing acetaminophen, 500 mg, dextromethorphan and pseudoephedrine and reports taking 2 tabs daily for 2 days. On day 28, the patient was found to have an ALT value of 1017, an AST value of 294, an ALP value of 134 (almost 3 times higher than baseline), and a total bilirubin value of 4.9. Apparently he took no additional acetaminophen or any herbal products. At the time, the patient reported transient fever and anorexia without abdominal pain. The study drug was apparently not discontinued. Serum enzymes rapidly returned to normal over the course

of 8 days as did the bilirubin value, and all values returned to normal on day 57 despite continuation of the study drug. Subsequent evaluation demonstrated negative values for hepatitis viruses A, B, C, and E, and normal values for LDH, prothrombin time, INR, total iron, TIBC, ferritin, carbohydrate deficient transferrin, and ANA.

*Comment: The liver abnormalities are unlikely to be attributable to the test drug since it was continued yet the abnormal liver tests nevertheless returned to normal. A specific cause for the injury is uncertain but is so closely related to the URI and treatment with acetaminophen that one may wonder whether in fact more acetaminophen was taken than was described or whether some other product not admitted to was taken as well.
[Classification = Unlikely.]*

MB102077-0088-70220 (Treatment Blind). The patient, a 47 year old white female with type 2 diabetes, hyperlipidemia, and hypertension, who is overweight and carries a diagnosis of nonalcoholic steatohepatitis, entered the trial receiving a drug blinded to type. She was also receiving metformin, glibenclamide, fexofenadine, sitagliptin, valsartan, and amlodipine. From the time of study initiation, she had modest elevations of her aminotransferase levels (ALT higher than AST), and normal levels of ALP and total serum bilirubin. Concern was raised because of a slightly higher increase in her ALT and AST levels on day 57 of treatment without a change in her ALP or bilirubin levels. The study drug was not terminated and the values returned immediately to her baseline abnormal aminotransferase levels. Evaluation soon after entering the trial had shown negative results of extensive screening for hepatitis A, B, C, and E, for EBV infection, and for autoimmune markers (ANA, ASMA, anti-LKM1). The patient remained asymptomatic throughout the treatment period.

Comment: Clearly, this patient did not develop hepatotoxicity. Although not proven by liver biopsy (or if done earlier, not reported), it seems appropriate to consider that she indeed does have nonalcoholic steatohepatitis and that the individual small spike in the already abnormal aminotransferase levels is merely part of the natural mild variations in this condition. [No evidence of hepatotoxicity, therefore, not classifiable as DILI.]

D1690C0010-1003-24 (Dapa). The patient is a 48 year old white female with type 2 diabetes, a benign breast nodule, diabetic retinopathy, and osteoarthritis. The patient was treated with dapagliflozin for 341 days and also received sitagliptin, metformin as well as glucosamine, methotrexate (for 23 days), leflunomide, diclofenac, folic acid, levofloxacin and enalapril. Absolutely NO other information was provided other than the serial results of ALT, AST, ALP, and bilirubin values. This showed intermittent increases in both the ALT and AST values with intervening normal values as well as normal serum bilirubin values. No results given for viral or autoimmune serology.

Comment: Insufficient information was provided to reach any diagnosis. My sense is that the abnormalities are not likely to be a consequence of receipt of dapa. The patient is in any case receiving a number of other drugs that have been implicated in causing liver injury in the past, although they were taken at varying times for varying lengths. History and more complete work-up needed before an etiology for the abnormalities can be defined. [Insufficient information to classify.]

D1690C00019-5719-6 (Dapa). The patient is a 71 year old white female with type 2 diabetes, hypertension, stable angina, coronary artery disease and dyslipidemia. She entered a clinical trial and received dapagliflozin for 161 days. She was also treated with insulin and received a variety of drugs during the course of therapy related to changes in the clinical condition during the course. These included acetylsalicylic acid, simvastatin, donepezil, haloperidol, vinpocetine, metamizole, cyanocobalamin, atropine, dobutamine, dopamine, epinephrine, heparin, hydroxyethylamidon, and electrolytes. On day 31 of treatment, the patient developed agitation and a cognitive disorder and was diagnosed with Alzheimer's syndrome. Liver chemistries remained completely normal throughout and the reason for the present consultation request is the finding of "transient hepatomegaly." Abdominal ultrasound was unrevealing. The patient subsequently developed atrial fibrillation and died.

Comment: This is not an instance of drug-induced liver injury. Patient's cause of death was apparently a consequence of myocardial infarction. [No evidence of hepatotoxicity, therefore, not classifiable as DILI.]

D1691C0003-3306-11 (Treatment Blind). The patient is a 64 year old white female with type 2 diabetes, hypertension, hypercholesterolemia and stable angina pectoris. Minimal information was provided. Per report, she is said to have started the study on blinded medication and other drugs relevant to a clinical problem that emerged during treatment. The patient's liver chemistries at baseline and through day 29 were all completely normal. On day 29, the patient was found to have an ALT value of 267, all other tests being normal. Moreover, the ALT value had returned to normal at the time of the next testing, day 34, and remained normal throughout the rest of the follow-up evaluation, even though the test medication continued. The patient had apparently developed herpes zoster on days 6 through 9 and had been started on treatment with acyclovir that might have been responsible for the single elevated ALT value (although other abnormal values might have been found had testing taken place earlier).

Comment: This is not drug-induced liver injury from the test drug but the single abnormality might have occurred from the use of acyclovir. Indeed, the test drug was continued despite the single spike and yet the ALT values returned to normal. [Classification = Unlikely.]

D1690C00018-201-8 [the “Argentina case”] (Dapa). The patient is reported to be a 71 year old man from Argentina with type 2 diabetes, hypertension, and prior myocardial disease who participated in a randomized, double-blind age-stratified, placebo-controlled phase III study to evaluate the efficacy and safety of dapagliflozin. He entered the trial on (b) (6) and treatment continued until (b) (6) (a little over 9 months) when it was discontinued because of the development of acute symptoms (see below) accompanied by the development of abnormal liver related chemistries.

Little information was supplied of his past medical history other than that he had diabetes, hypertension and had suffered a myocardial infarction. Also he had a bundle branch block and had had a pacemaker inserted. The medications he was receiving included acetylsalicylic acid, metformin, losartan, atenolol, and carvedilol; exact start and stop dates for each medication are not given.

At the time of study entrance, his liver chemistries are reported to have been normal although his alkaline phosphatase values were slightly elevated.

	ALT	AST	AP	T/D Bili
(b) (6)	N	N	180	N
	-	-	164	-
	-	-	156	-

On (b) (6) the patient developed nausea, vomiting and diffuse non-colicky abdominal pain and was admitted to the coronary unit for evaluation and his test medication was discontinued. He’d had no chest pain or dyspnea. His daughter later reported that he had attended a family party on the weekend (presumably just preceding his admission to the hospital) where he consumed alcohol (amount not indicated) and that his symptoms had begun in the late afternoon and evening (but no information on the precise relationship to the alcohol intake is stated). No other information on his general use of alcohol is given. On admission, his temperature, blood pressure and pulse were normal and he was tender to deep palpation in his epigastrium and right upper quadrant but apparently had no rebound tenderness. He was moderately cognitively impaired but no further description of this phenomenon is presented. He is not reported to have tremors or asterixis. His EKG did not reveal evidence of new cardiac disease. His initial liver-related chemistries (b) (6) showed an ALT value of 150, an AST of 262, an alkaline phosphatase (AP) value of 547 and a total serum bilirubin value of 1.7. His white blood cell count was 7300 and his hematocrit was 35%. The initial diagnosis was that of biliary colic, and an ultrasound was performed the next day that was suboptimal because he was apparently unable to hold his breath during the procedure. A liver US performed later (b) (6) was reported to show hepatic and pancreatic steatosis; no comment is made regarding the biliary tree or whether or not gall stones were visualized. His amylase at this time was 184 and his liver-related tests showed worsening with now an elevated serum bilirubin that appears to be a

predominantly indirect hyperbilirubinemia. However, his hematocrit had not worsened. Additional workup for viral infection revealed negative tests for hepatitis A, B, and C. He was treated with IV hydration, hyocine, metaclopramide, ranitidine, enoxaparin and simvastatin. By the next day, his abdominal examination demonstrated less pain on palpation, and within 3 days, his bilirubin value had dropped considerably returning to normal by the next day (b) (6). Thus, over a period of 4 days, his total bilirubin value dropped from a peak (b) (6) of 5.15 to a 0.9 (b) (6). He was transferred from the cardiology unit to the general medical ward. It is noted that at the time of enrollment, his weight was 77 kg that had dropped to 67.5 kg (b) (6).

	ALT	AST	AP	T/D Bili	Amylase
(b) (6)	150	262	547	1.7/	
	504	613	607	4.3/1.3	
	287	179	515	5.15/1.0	
	133	43	547	1.39/0.46	
	101	57	577	0.9/0.37	
	66	N	290	N	
	189	61	433	1.9/0.8	
	148	22	338	1.3/	

No further follow-up, needed to help entertain a diagnosis, is available at this time but is clearly needed particularly since there seems to be a secondary rises in his serum enzyme (ALT, AST, AP) values but not his serum bilirubin value.

Comment: This 71 year old man develops nausea, vomiting, and abdominal pain a little over 9 months after starting the use of dapagliflozin and a day or two after having consumed alcohol although the amount consumed is not reported nor is his past history of alcohol use. He is found to have abnormal liver chemistries with an initial pattern of mixed hepatocellular/cholestatic liver disease together with an increase in serum bilirubin that is predominantly indirect reacting. A day later, all of his values worsen a little although it now assumes a pattern of cholestatic liver disease, with his increased serum bilirubin value remaining predominantly indirect. Within 2 days, his bilirubin value drops considerably although his AP value remains elevated. Five days later, his AST and serum bilirubin value has become normal while his ALT and AP values have markedly improved but are not back to normal. Two weeks later, there is a secondary spike in serum enzymes and serum bilirubin that show some improvement one week later but when last seen continue to be abnormal. Of vital importance is the need for further follow-up.

The exact cause for the liver dysfunction in this patient is not entirely clear. Potential etiologies include acute biliary tree disease, acute alcoholic hepatitis, acute pancreatitis, Gilbert disease overlay, and drug-induced liver injury.

In favor of biliary tree disease is the acute development onset of nausea and vomiting together with abdominal and right upper quadrant tenderness associated with abnormal liver chemistries that have a pattern of cholestatic liver disease. Moreover, the diagnosis is suggested by an abrupt drop in the serum bilirubin value (suggesting the pulling of a plug) although the elevated bilirubin values are largely indirect- rather than direct-acting. Finally, it appears that the patient has a secondary increase in liver-related abnormalities although not reported to be associated with symptoms such as fever and/or abdominal pain. Items not in support are the lack of fever or leukocytosis on both occasions and the lack of a positive diagnosis of dilated biliary tracts or of evidence of gallstones on US examination.

Acute alcoholic hepatitis needs to be considered in the differential because of the history of a possible alcoholic binge just before developing liver disease (although there is no history of chronic alcoholism and no information on the amount of alcohol consumed just before liver disease onset), and the evidence on US of fat in the liver and pancreas. But this diagnosis seems less likely because of the height of serum enzymes, particularly of the ALT that rarely exceeds a value of 150 in alcoholic hepatitis unless accompanied by other diseases or by acute or chronic pancreatitis (but the serum amylase was not particularly elevated), the later enzyme ratios where the ALT elevation exceeded the AST elevation (usually the reverse in alcoholic hepatitis), and the lack of leukocytosis, as well as by the quite rapid improvement and then apparently spontaneous worsening without mention of further drinking.

Acute pancreatitis could account for nausea, vomiting and abdominal pain., particularly if the patient was a chronic alcoholic with a recent binge; acute or chronic pancreatitis is sometimes accompanied by abnormal liver chemistries, especially if the affected person also has underlying chronic alcoholic liver disease. The amylase value does not support this diagnosis nor does the lack of US evidence of chronic pancreatitis. Again, an alcohol history or a history of previous biliary tree problems are needed.

The bilirubin pattern shows an increase that is largely indirect, raising the issues of underlying Gilbert's disease precipitated by the acute liver injury or hemolysis. With regard to the latter, there is no evidence of falling hemoglobin nor is there an abnormal haptoglobin. As for Gilbert's disease, this condition would not itself account for the abnormal liver chemistries and not all values fall into the indirect range. Still, it cannot be entirely excluded as a contributing factor.

Drug-induced liver injury also cannot be completely excluded either but seems unlikely because of the protracted latency of over 9 months between starting the drug and developing overt evidence of liver disease, the short duration of liver injury, particularly the abrupt reduction in serum bilirubin values, as well as the secondary spike without restarting the drug.

Also to be explained is why he lost 9.5 kg in weight over a period of 9 months; was he on an active diet aimed at losing weight or can the weight loss be accounted for by his underlying "liver" disease?

No definitive conclusion can be reached without learning about the patient's alcohol intake history, whether he has suffered previously from biliary tree disease, whether he carries a known diagnosis of Gilbert's disease, what previous diseases he has suffered, whether he was on a weight-losing diet, and importantly, what the outcome is or will be of the current bout of liver disease."

Addendum: *As noted in the INTRODUCTION, upon initial review, I concluded that, although I thought that drug-induced liver injury from dapagliflozin was unlikely, I felt that with the addition of more information, it might be possible to reach an alternative diagnosis. I therefore asked for certain specific information that included the following: a past history that might suggest the existence of biliary tree disease; a past history of potential alcoholism; an explanation for the patient's weight loss; an explanation for the transient reappearance of liver dysfunction, seeking specifically data that might support the passage of a gallstone; and an explanation for a disparity of serum bilirubin values shown on two separate reports.*

*The additional sought data have now been supplied by the sponsor. They indicate that there are no prior data to suggest biliary tree disease that represented for me a potential alternative diagnosis. The cause for the slight increase in biochemical dysfunction toward the end of the follow-up does not appear to be a consequence of the passage of a stone or a recurrence from the drug since it was not re-started. Although there is a lack of certainty, the likeliest basis for the observed liver-related abnormalities would seem to be acute alcoholic hepatitis even though it is stated that he was not a heavy drinker and the ratio of raised ALT to raised AST values did not follow the typical pattern. Regardless, the additional data supplied do NOT add to the possibility that the liver disease was a consequence of dapagliflozin hepatotoxicity.
[Classification = Unlikely.]*

SUMMARIZATION

This addendum document includes review of 7 cases of putative liver injury in the setting of the dapagliflozin clinical development program. These cases, with adjudication for DILI due to dapagliflozin, are outlined in the following table.

Patient ID	Treatment	DILI Classification
MB102029-4-276	Dapagliflozin	Unlikely
MB102054-24-498	Blinded	Unlikely
MB102077-88-70220	Blinded	Not DILI
D1690C00010-1003-24	Dapagliflozin—no narrative	Insufficient information
D1690C00019-5719-6	Dapagliflozin	Not DILI
D1691C00003-3306-11	Blinded	Unlikely
D1690C00018-201-8	Dapagliflozin	Unlikely

The previous DPV review of cases from the dapagliflozin clinical development program included one case consistent with Hy’s Law that was assessed as **Probably** related to dapagliflozin. This series of 7 cases includes a much broader range of liver injury - including cases with very limited evidence for an hepatotoxicity – none of which were assessed at even the **Possible** level in relation to the study drug (including control/placebo and dapagliflozin treatments).

As noted in the previous review, assessing the likelihood of hepatotoxicity is a difficult problem and in general is based on identifying liver dysfunction that develops within a few days to up to six months after starting a drug that does not appear to be a result of other conditions that cause liver disease and that may mimic drug-induced liver disease (DILI). Thus it can be viewed as a “diagnosis of exclusion.” Accordingly, this requires that in clinical trials when liver injury is observed, as outlined in the CDER Guidance document, all other conditions that can mimic DILI are sought and excluded. Even after concluding that DILI is the probable cause after excluding potentially competing causes, identifying the specific drug, herbal, or dietary supplement can be challenging if, in fact, more than one or even numerous products are being received. Selecting a specific product takes into account an appropriate temporal relationship between the start of the drug and the first identification of possible liver disease (based generally on the development of increased serum enzymes or bilirubin levels or on appropriate symptoms) as well as considering the past history of the drug with regard to its potential for causing hepatotoxicity.

CONCLUSION

This review is limited to assessment of 7 additional case reports and does not attempt to review all potential data streams available to assess the risk of hepatotoxicity with dapagliflozin. Based on inspection of Table 1 (page 8) of the sponsor's hepatic Adjudication Report dated 25 October 2011, the HAC has assessed a total of 8 cases of concurrent ALT elevation and bilirubin elevation and placed all cases at the level of Possible (n=3), or lower. To date, DPV is aware of one case - D1690C00004-4402-6 (adjudicated in the first review¹) - classified as a **Probable** Hy's law case in association with dapagliflozin.

In further analyses shown in Table 1, the sponsor also concludes that there is no imbalance in hepatic events between dapagliflozin and control arms up to the data lock date of 15 July 2011.

At this time, no recommendation can be advanced for any change in the assessment of the hepatotoxic potential of dapagliflozin or for enhanced vigilance for hepatotoxicity within the dapagliflozin clinical development program.

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/s/

MARGARITA V TOSSA
11/21/2011

ALLEN D BRINKER
11/21/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 26, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Tarek Hammad, MD, PhD, MSc, MS, Deputy Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER
Diane K Wysowski, PhD, MPH, Team Leader
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: (b) (4)

Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-3281

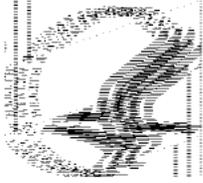
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/s/

JING JU
09/26/2011

TAREK A HAMMAD
09/28/2011



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: September 22, 2011 **Date Consulted:** August 10, 2011

From: Tammie Howard, RN, MSN
Regulatory Reviewer
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Karen Feibus, MD
Clinical Team Leader
Pediatric and Maternal Health Staff, Maternal Health Team

Lisa Mathis, MD
Associate Director, Office of New Drugs

To: Division of Metabolism and Endocrinology Products (DMEP)

Drug: Dapagliflozin NDA 202293

Subject: New NDA (NME-First in Class) submission

**Materials
Reviewed:** Dapagliflozin labeling

**Consult
Question:** Please review labeling and comment regarding:
1. What pregnancy category does the MHT recommend?
2. What labeling recommendations does the MHT have for section 8.1 of the dapagliflozin labeling?

INTRODUCTION

NDA 202293 for dapagliflozin, a new molecular entity (NME), was submitted by Bristol-Myers Squibb (BMS) on December 28, 2010. The proposed indication for dapagliflozin is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor, and if approved, would be a first-in-class treatment for Type 2 Diabetes. SGLT2 is the major transporter that is responsible for reabsorption of glucose in the kidney. Dapagliflozin inhibits the reabsorption of glucose, without acting on insulin secretion or action, providing for elimination of glucose by the kidney, reducing plasma glucose.

On August 10, 2011, the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) was consulted by the Division of Metabolism and Endocrinology Products (DMEP) to review the dapagliflozin labeling and provide comment regarding the pregnancy and nursing mothers section of labeling. In addition, the PMHS-MHT was asked for a recommendation regarding the appropriate pregnancy category for this drug.

BACKGROUND

According to the American College of Obstetricians and Gynecologist Clinical Management Guidelines¹ there are more than eight million women in the United States with pre-gestational diabetes mellitus. Diabetes mellitus (DM) type 2 is chronic condition where the body does not produce enough insulin or resists the effects of insulin, resulting in an inability to maintain normal blood sugar (glucose) in the body. There is no cure for DM type 2 and patients with DM type 2 usually require treatment with medication at some point to manage the condition. In addition to treatment with insulin, there are numerous oral and injectable medications available, most of which affect insulin production or insulin action in the body².

Glucose is filtered by the kidney, and normally, about 99% of filtered glucose is reabsorbed into plasma via the proximal tubules of the kidney. SGLT2 is a transporter for glucose from the tubules into tubular epithelial cells, and about 90% of glucose is reabsorbed by the kidney via SGLT2³. Dapagliflozin inhibits the reabsorption of glucose, reducing plasma glucose levels without a direct effect on insulin production or insulin action.

Dapagliflozin demonstrated efficacy and safety in animal and clinical trials. However, in animal reproductive studies, increased incidence and/or severity of renal pelvic and tubular dilatations occurred in the offspring of pregnant rats following maternal dapagliflozin exposure during times of pregnancy and lactation that generally correspond to times of human renal development and

¹ Pregestational Diabetes Mellitus. ACOG Practice Bulletin No. 60. American College of Obstetrician and Gynecologist 2005;105:675-685.

² Mayo Foundation for Medical Education and Research (MFMER). Type 2 Diabetes. May 24, 2011 available at: <http://www.mayoclinic.com/health/type-2-diabetes/DS00585>

³ Ghosh, RK, Ghosh SM, Chawla S, Jasdanwala SA. SGLT2 Inhibitors: A New Emerging Therapeutic Class in the Treatment of Type 2 Diabetes Mellitus. The Journal of Clinical Pharmacology 2011 published online May 4, 2011.

maturation (second and third trimester of pregnancy). In addition, similar outcomes were observed in the renal development of rat offspring with direct dapagliflozin exposure. Human kidney maturation occurs in utero and continues through the first two years of life. Based on these reproductive animal study outcomes, there is potential risk to the human fetus and in nursing infants.

This review provides MHT recommendations and comment regarding the Warnings and Precautions (5), Pregnancy (8.1), Nursing Mothers (8.3) and Patient Counseling (17) sections the sponsor's proposed labeling and the appropriate pregnancy category.

REVIEW OF SUBMITTED MATERIAL

Sponsor's proposed labeling:

(b) (4)



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/s/

TAMMIE B BRENT HOWARD
09/22/2011

Karen B FEIBUS
09/23/2011

I concur with the labeling recommendations provided in this review.

LISA L MATHIS
09/25/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 9, 2011

To: Mary H. Parks, MD
Director, Division of Metabolism and Endocrinology Products
Office of New Drugs

Through: Tarek Hammad, MD, PhD, MSc, MS
Deputy Director, Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Diane K. Wysowski, PhD, MPH
Team Leader, Division of Epidemiology I

From: Christian Hampp, PhD
Visiting Associate/Epidemiologist,
Division of Epidemiology I

Subject: [REDACTED] (b) (4)

Drug Name(s): Dapagliflozin

Submission Number: eCTD sequence # 44 and 47

Application Type/Number: NDA #202-293

Applicant/sponsor: Bristol-Myers-Squibb and AstraZeneca

OSE RCM #: 2011-3282

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/s/

CHRISTIAN HAMPP
09/09/2011

TAREK A HAMMAD
09/09/2011

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 29, 2011

TO: Mehreen Hai, Regulatory Project Manager
Somya (Verma) Dunn, Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance

SUBJECT: Evaluation of Clinical Inspections

NDA: 202293

APPLICANT: Bristol-Myers Squibb

DRUG: Dapagliflozin

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

CONSULTATION REQUEST DATE: March 16, 2011

DIVISION ACTION GOAL DATE: October 28, 2011
PDUFA DATE: October 28, 2011

I. BACKGROUND:

Bristol Myers Squibb (BMS) submitted NDA 202293 for the use of Dapagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with Diabetes Mellitus Type 2. Dapagliflozin, a new molecular entity, is an orally administered active inhibitor of sodium-glucose transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. BMS co-developed the product with AstraZeneca (AZ). OSI received a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of the indication. The review division requested inspection of the following 4 pivotal studies sponsored by BMS:

- A. Protocol MB102013 entitled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise”
- B. Protocol MB102014 entitled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin Alone”
- C. Protocol MB102030 entitled “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone”
- D. Protocol MB102034 entitled “A Multicenter, Randomized, Double-Blind, Active Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg in Combination with Metformin as Initial Therapy as Compared with Dapagliflozin 10 mg Monotherapy and Metformin Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control.”

The review division requested inspection of the following 2 pivotal studies sponsored by AZ:

- E. Protocol D1690C00006 entitled “A 24-Week International, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Phase III Study with a 24-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin Therapy When Added to the Therapy of Patients with Type 2 Diabetes with Inadequate Glycemic Control on Insulin”
- F. Protocol D1690C00004 entitled “A 52-Week International, Multi-centre, Randomized, Parallel-group, Double-blind, Active-controlled, Phase III Study with a 52-Week Extension Period to Evaluate the Efficacy and Safety of Dapagliflozin in Combination with Metformin Compared with Sulphonylurea in Combination with Metformin in Adult Patients with Type 2 Diabetes Who have Inadequate Glycemic Control on Metformin Therapy Alone.”

Three domestic clinical investigator sites, four foreign clinical investigator sites, and both sponsors were inspected in support of this application. Clinical site selection was on the basis of relatively high enrollment and, except for Dr. Mitchell's site, participation in more than one of the above trials.

II. RESULTS (by Site):

Name of Clinical Investigator (CI), or Sponsor & Location	Protocol #/ # Subjects Randomized	Inspection Date	Final Classification
CI: Rubin H. Saavedra, M.D. Nevada Alliance Against Diabetes 1440 N. Eastern Ave Las Vegas, NV 89101	MB 102013/14S MB 102014/12S	April 26 to May 19, 2011	VAI
CI: Rafael Montoro, M.D. Clinical Therapeutics Corporation 470 Biltmore Way Suite 102 Coral Gables, FL 33134	MB 102030/14S MB 102034/24S	May 12 to June 2, 2011	VAI
CI: Jerry Ray Mitchell, M.D. Texas Ctr. For Drug Development 6550 Mapleridge Ste. 201 Houston, TX 77081	MB 102034/18S	May 19 to May 25, 2011	VAI
CI: Laura Maffei, M.D. Consultorios Asociados de Endocrinología Cervino 3365/75, Piso 1, Office 2 Buenos Aires, Argentina	MB102014/12S D1690C00004/30S	June 13 to 17, 2011	NAI
CI: Maria Rosa Ulla Centro Privado de Endocrinología Osteología y Metabolismo Damaso Larranaga 94, Córdoba X5000BNB, Argentina	MB102030/16S D1690C00004/21S	June 6 to 10, 2011	NAI
CI: Ronald Goldenberg LMC Endo. Centres (Thornhill) Ltd. 531 Atkinson Ave. Ste. 17 Thornhill, ON L4J 8L7 Canada	MB102013/11S D1690C00006/18S	June 13 to 17, 2011	NAI
CI: Guy Tellier Omnispec Clin. Res. Inc. 13714 Du Cure-Labelle, Ste. 101 Mirabel, QC J7J 2K8, Canada	MB102014/5S D1690C00006/ 9S	June 20 to 23, 2011	NAI
Sponsor: Bristol-Myers Squibb Route 206 & Providence Line Princeton, NJ 08543	MB 102013/25S MB 102014/29S MB 102030/30S MB 102034/42S	July 19 to 27, 2011	Pending (Preliminary classification VAI)
Sponsor: AstraZeneca GmbH Tinsdaler Weg 183, 22880 Wedel, Germany	D1690C00004/ 41S D1690C00006/ 27S	June 27 to 30, 2011	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.1. **Rubin H. Saavedra, M.D.**

Nevada Alliance Against Diabetes, 1440 N Eastern Ave, Las Vegas, NV 89101

- a. **What was inspected:** At this site, for Protocol MB102013, a total of 25 subjects were screened, 14 subjects were enrolled and randomized, 9 subjects completed the short term phase of the study, and 2 completed the long term phase of the study. For Protocol MB102014, a total of 23 subjects were screened, 12 subjects were enrolled and randomized, 8 subjects completed the short term phase of the study, and 3 completed the long term phase of the study. An audit of 12 subjects' records was conducted for Protocol MB102013, and an audit of 14 subjects' records was conducted for Protocol MB102014. This included case report forms, progress notes, regulatory binder, and IRB correspondence and laboratory reports.
- b. **General observations/commentary:** Form FDA 483 was issued for violations including: failure to list a subinvestigator on Form 1572, protocol violations concerning lack of obtaining orthostatic blood pressure (standing vital signs were taken before supine vital signs) and of repeating hematology and chemistry blood work for initial inadequate samples, and inadequate drug accountability. Concerning the orthostatic blood pressure, this was found to occur for two of the subjects for Protocol MB102013 and five of the subjects for Protocol MB102014. All subjects appear to have had at least two determinations that were taken according to the protocol requirements, and therefore this finding is unlikely to impact assessment of the data. Concerning the blood work, these were isolated chemistry and hematology values that were not redrawn when samples were found to be inadequate. These subjects had normal values for these laboratory tests drawn at other visits. The inadequate drug accountability concerned clerical reconciliation and did not result in missassignment of randomized treatment. There is documentation to support that subjects were adequately dispensed drug, and this finding is unlikely to impact data validity. These violations did not impact adversely on data integrity or subject safety. During the trial, the clinical site was blinded to HbA1C values except for rescued subjects. The HbA1C values could be verified for subject eligibility and for rescued subjects. There was no under-reporting of adverse events. Dr. Saavedra adequately responded to the inspection findings in a letter received by FDA on June 10, 2011.
- c. **Assessment of data integrity:** The above findings are considered minor and unlikely to impact data reliability. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Rafael Montoro, M.D.

Clinical Therapeutics Corporation
470 Biltmore Way Suite 102, Coral Gables, FL 33134

- a. **What was inspected:** At this site, for Protocol MB102030, a total of 26 subjects were screened, 14 subjects were randomized, and 8 subjects completed the study. There were no SAEs or deaths reported and no subjects discontinued from the study because of adverse events (AEs) or were lost to follow-up. Subject 00376 discontinued due to lack of efficacy. For Protocol MB102034, a total of 27 subjects were screened, 24 subjects were randomized, and 16 subjects completed the study. There was one SAE reported of a myocardial infarction experienced by Subject 0697. There were no deaths reported and no subjects discontinued because of AEs or lack of efficacy. A total of 4 subjects were listed as lost to follow-up.

An audit of 8 enrolled subjects' records and 2 screen failure subjects' records was conducted for Protocol MB102030, and an audit of 10 enrolled subjects' records and 2 screen failures was conducted for Protocol MB102034. This included authority and administration of the study, the protocols, case report forms, progress notes, regulatory binder, and IRB correspondence and laboratory reports.

- b. **General observations/commentary:** A Form FDA 483 was issued to Mary Lou Maguire, President and sole owner of Clinical Therapeutics Corporation, the entity where the clinical trials were conducted, for failing to report two adverse events that occurred in conduct of Protocol MB 102030. These were failing to report a triglyceride value of 1933 mg/dL for Subject 045 that occurred on 1/24/09, and failing to report a magnesium level of 1.0meq/l for Subject 00109 that occurred on 10/06/09. Ms. Maguire adequately responded on behalf of Clinical Therapeutics Corporation to the inspection findings in a letter dated June 15, 2011. As noted above, there were 2 instances of abnormal laboratory values that were not reported as AEs. Otherwise, there was no evidence of underreporting of AEs. The clinical sites were blinded to the primary endpoint data for HbA1C after the baseline value except when subjects were rescued. For Protocol MB102030, the HbA1C was verified for all 3 subjects that were rescued, Subjects 045, 109, and 346. For Protocol MB102034, the HbA1C was verified for the 3 rescued subjects for whom records were audited, Subjects 256, 861, and 962.
- c. **Assessment of data integrity:** The lack of reporting of the 2 abnormal laboratory values as adverse events is considered an isolated occurrence and unlikely to impact data reliability. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. **Jerry Ray Mitchell, M.D.**
Texas Ctr. For Drug Development, 6550 Mapleridge Ste. 201, Houston, TX 77081
 - a. **What was inspected:** For Protocol MB102034, at this site, 25 subjects were screened, 18 subjects were randomized, and 11 subjects completed the study. One subject required rescue and discontinued from the study. An audit of 6 subjects' records was conducted.
 - b. **General observations/commentary:** A Form FDA 483 was issued because the investigational drug disposition records were not adequate. Specifically, for two subjects, the subject diaries concerning test article intake did not match the reported number of pills taken on the eCRF. The site stated that this was because the actual number of pills in the returned bottles counted by study staff, not the subject diaries, was used to determine drug intake because the diaries were considered less accurate than the pill counts. However, there was no note to file to document this occurrence. This finding was not considered to significantly impact data integrity or subject safety. Dr. Mitchell responded adequately to the inspection findings in a written correspondence received by FDA on June 14, 2011. There was no evidence of under reporting of adverse events. The clinical sites were blinded to the primary endpoint data for HbA1C after the baseline value except when subjects were rescued.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
4. **Laura Maffei, M.D.**
Consultorios Asociados de Endocrinologia, Cervino 3365/75, Piso 1, Office 2
Buenos Aires, Argentina
 - a. **What was inspected:** At this site, for Protocol D1690C00004, a total of 81 subjects were screened. Forty-seven subjects enrolled into the study, and 30 were randomized. Sixteen subjects discontinued the study. The study is ongoing, with 14 subjects continuing on in the study. For Protocol MB102014, a total of 25 subjects were screened, 13 subjects were enrolled, and 12 subjects were randomized. A total of four subjects discontinued from the study. For Protocol D1690C00004, a review of 100% of informed consent documents was performed for 15 subjects. An audit of 32 subjects' records was conducted. For Protocol MB102014, an audit of 14 subjects' records was conducted. The review included a comparison of source documentation and electronic case report forms (CRFs) with data listings submitted to the NDA. Specific records reviewed included, but were not limited, to adverse event reporting, inclusion/exclusion criteria, ICF documents, test article accountability, and adherence to protocol-specified procedures for blinding and randomization.

- b. **General observations/commentary:** No violations were cited and a Form FDA 483 was not issued. During the trials, the clinical site was blinded to HbA1C values except for determination of eligibility and for subjects whose values were above the prespecified levels in the protocols. The HbA1C values could be verified for subject eligibility and for rescued subjects. There was no evidence of under-reporting of adverse events. During the sponsor inspection it was determined that postural vital signs were not determined according to the protocol. See the discussion below under the BMS inspection results.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. **Maria Rosa Ulla, MD**

Centro Privado de Endocrinología, Osteología y Metabolismo
Damaso Larranaga 94, Córdoba, X5000BNB, Argentina

- a. **What was inspected:** At this site, for Protocol D1690C00004 a total of 35 subjects were screened. Twenty-six subjects enrolled into the study and 21 were randomized. Ten subjects discontinued the study. The study is ongoing, with 11 subjects continuing on in the study. For Protocol MB102030, at total of 36 subjects were screened, and 16 subjects were enrolled and randomized. One subject discontinued from the study. For Protocol D1690C00004 a review of the informed consent documents was performed for 5 subjects. An audit of 16 subjects' records was conducted. For Protocol MB102030, an audit of 18 subjects' records was conducted. The review included a comparison of source documentation and electronic case report forms (CRFs) with data listings submitted to the NDA. Specific records reviewed included, but were not limited to adverse event reporting, inclusion/exclusion criteria, ICF documents, test article accountability, monitoring records, and adherence to protocol-specified procedures for blinding and randomization.
- b. **General observations/commentary:** No violations were cited and a Form FDA 483 was not issued. During the trials, the clinical site was blinded to HbA1C values except for determination of eligibility and for subjects whose values were above the prespecified levels in the protocols. The HbA1C values could be verified for subject eligibility and for rescued subjects. There was no evidence of under-reporting of adverse events.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

6. **Ronald Goldenberg, MD**
LMC Endocrinology Centres (Thornhill) Ltd., 531 Atkinson Ave. Suite 17,
Thornhill, ON L4J 8L7 CN
- a. **What was inspected:** At this site, for Protocol D1690C00006, a total of 29 subjects were screened. Eighteen were randomized. Seven subjects discontinued the study and 11 completed the study. For Protocol MB102013, a total of 14 subjects were screened, and 11 subjects were randomized. A total of six subjects discontinued from the study and 5 subjects completed the study.
- b. **General observations/commentary:** No violations were cited and a Form FDA 483 was not issued. There was no evidence of under-reporting of adverse events. Because the site was blinded to HbA1c for subjects after randomization, the primary efficacy endpoint was verified by comparison of the data listings from the NDA with a listing supplied at the clinical site by the sponsor.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
7. **Guy Tellier, M.D.**
Omnispec Clin. Res. Inc. ,13714 Du Cure-Labelle, Ste. 101
Mirabel, QC J7J 2K8, Canada
- a. **What was inspected:** At this site, for Protocol D1690C00006, a total of 15 subjects were screened. A total of 9 subjects were enrolled and 5 subjects completed the study. For Protocol MB102014, a total of 5 subjects were screened, randomized and completed the study. For Protocol D1690C00006 and Protocol MB102014 a review of 100% of informed consent documents was performed for all the subjects screened. For Protocol D1690C00006 an audit of the 9 randomized subjects' records was conducted. For Protocol MB102014, an audit of the 5 randomized subjects' records was conducted. The review for both protocols included a comparison of source documentation and electronic case report forms (CRFs) with data listings submitted to the NDA. Specific records reviewed included, but were not limited, to adverse event reporting, inclusion/exclusion criteria, ICF documents, test article accountability, and adherence to protocol-specified procedures for blinding and randomization.
- b. **General observations/commentary:** No violations were cited and a Form FDA 483 was not issued. There was no evidence of under-reporting of adverse events. Because the site was blinded to HbA1c for subjects after randomization, the primary efficacy endpoint was verified by comparison of the data listings from the NDA with a listing supplied at the clinical site by the sponsor.

- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

8. **AstraZeneca GmbH**

Tinsdaler Weg 183, 22880 Wedel, Germany

- a. **What was inspected:** This inspection covered sponsor activities for Protocol D1690C00004 and Protocol D1690C00006, and focused on the following clinical investigators: Dr. Laura Maffei, Dr. Maria Rosa Ulla, Dr. Guy Tellier, and Dr. Ronald Goldenberg. For Protocol D1690C00004, because there were a relatively high number of sites in South Africa, the inspection also reviewed the following sites in South Africa: Drs. Lesley Burgess, Asad Bhorat, Muhammad Moosa, and Trevensan Padyachee. The inspection reviewed the following: organizational duties and responsibilities, CRO contracts, sponsor SOPs, site selection, pharmacovigilance, monitoring program, training program, sponsor-clinical site correspondence, sponsor site audits, adjudication committee correspondences, DSMB correspondences, IRB/informed consent, randomization procedures, data management and drug accountability.
- b. **General observations/commentary:** The clinical sites noted above appear to have been adequately monitored during the clinical trials. AstraZeneca appears to have executed sponsor responsibilities pertinent to sponsored studies adequately. No regulatory violations were noted and no Form FDA 483 was issued.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

9. **Bristol-Myers Squibb**

Route 206 & Providence Line, Princeton, NJ 08543

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report.

- a. **What was inspected:** This inspection covered sponsor activities for Protocols MB102013, MB102014, MB102030 and MB102034. The inspection focused on the following clinical investigators: Dr. Rubin Saavedra, Dr. Rafael Montoro, Dr. Jerry Ray Mitchell, Dr. Laura Maffei, Dr. Maria Rosa Ulla, Dr. Guy Tellier, and Dr. Ronald Goldenberg. The inspection reviewed the following: organizational duties and responsibilities, CRO contracts, sponsor SOPs, site selection, pharmacovigilance, monitoring program, training program, sponsor-

clinical site correspondence, sponsor site audits, adjudication committee correspondences, DSMB correspondences, IRB/informed consent, randomization procedures, data management and drug accountability.

- b. **General observations/commentary:** A Form FDA 483 was issued for violations concerning monitors failing to ensure that the studies were conducted according to the investigational plan. These findings were cited because the monitors did not bring clinical investigators into compliance concerning the violations. The most significant regulatory violations were the following:
1. Postural vitals signs (VS) were not conducted correctly at 5/9 studies. Postural VS were required at visits Day 1, Weeks 1, 12, 24, 50 and 102 (for those long term studies). For most sites the violations were sporadic, occurring on one or two of these visits in about one-third of subjects, so that during the course of the study, all subjects had at least one postural VS determined at or after week 12 except one subject at Dr. Maffei's site. It seems that the most violations occurred at the Ulla and Maffei sites.
 2. The inspection report notes 4 instances in which urine culture was not obtained in violation of the protocol requirement that symptoms suggestive of urinary tract infection should have documented urine cultures. All the adverse events (AEs) were captured in the line listings, and there was no evidence of under reporting of AEs.

Reviewer comment: The CI specific protocol violations noted during the BMS inspection were not noted during the inspections of the clinical sites for Drs. Maffei, Ulla, Goldenberg, and Tellier. It is unclear from the Establishment Inspections Reports (EIRs) why the protocol violations were not noted. The violations may have not been identified during the inspections or may not have been considered significant. However, given that the violations were sporadic in nature, it is unlikely that these findings would impact data reliability. Further, this was confirmed based on discussions with the review division.

The sponsor responded adequately to the violations in a letter dated August 10, 2011. Specifically, for the orthostatic blood pressure measurements, BMS noted that the various protocols were associated with different case report forms, only some of which documented the time at which the vital signs were taken. At some sites there were violations and at other sites, the source documents were able to provide evidence that the vital signs were obtained in the appropriate order. BMS stated that they will redesign CRFs and instruct monitors to train and reinforce procedures for the site staff. BMS also noted that the requirement for obtaining urine cultures was instituted in an amendment to the protocol in which the primary purpose was to alert clinical sites to liver toxicity.

These findings were discussed with the review division in a series of e-mails and conversations during August 2011. The review division noted that, for the

postural vital signs, given that the violations were not widespread and that the symptoms of hypovolemia and dehydration would have been captured in AE reporting, the risk of possible dehydration related to the product appears to have been adequately captured in the data submitted to the NDA. Similarly, AEs concerning the urinary system appear to have been adequately captured and the urine cultures were not a requirement to capture these events.

- c. **Assessment of data integrity:** The sponsor was cited for violations concerning monitoring protocol adherence. These protocol violations do not appear to have a significant impact on data integrity because the data collected concerning dehydration and urinary tract symptoms was adequately captured by the reporting of adverse events. Notwithstanding the inspectional observations noted above, the studies appear to have been conducted adequately, and the data submitted by this sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Seven clinical investigator sites and two sponsor sites were inspected in support of this NDA. Inspection of clinical investigators Drs. Maffei, Ulla, Goldenberg, and Tellier did not note any violations although it should be noted that the inspection of the sponsor BMS indicated that some violations concerning the procedures for obtaining postural vital signs and urine cultures occurred at the Maffei and Ulla sites. As noted above, the significance of these findings was discussed with the review division, and it was determined that these violations did not significantly impact data integrity. Inspection of AstraZeneca, one of the sponsors, did not note any violations. Inspection of Dr. Saavedra noted violations concerning lack of obtaining orthostatic blood pressure (standing vital signs were taken before supine vital signs) and of repeating hematology and chemistry blood work for initial inadequate samples, and inadequate drug accountability in an isolated number of subjects. Inspection of Dr. Montoro noted failure to report 2 abnormal laboratory values as adverse events. Inspection of Dr. Mitchell noted inadequate investigational drug disposition records. Inspection of Bristol-Myers Squibb noted violations concerning adequacy of monitoring of the clinical trials as discussed above. The violations cited for the inspection of these 3 clinical sites and the sponsor, BMS, did not appear to be systemic or widespread in nature, and unlikely to significantly impact data reliability. In discussion with the review division, it was determined that these violations did not appear to have a significant impact on data integrity.

The data are considered reliable in support of the application.

Note: The final classification for the inspection of BMS is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after receipt and review of the EIR for this inspection.

{See appended electronic signature page}

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 20 July 2011

To: Mary H. Parks, MD
Director, Division of Metabolism and Endocrinology Products
Office of New Drugs

Through: Solomon Iyasu, MD, MPH
Director, Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Diane K. Wysowski, PhD, MPH
Team Leader, Division of Epidemiology I

From: Christian Hampp, PhD
Visiting Associate/Epidemiologist,
Division of Epidemiology I

Subject: Updated Analysis - Incidence of Bladder Cancer in a Diabetic
Population

Drug Name(s): Dapagliflozin

Submission Number: n/a

Application Type/Number: IND 068652
NDA 202293

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1476

UPDATED ANALYSIS – INCIDENCE OF BLADDER CANCER IN A DIABETIC POPULATION

1 BACKGROUND

My previous review (Hampp C., Incidence of Bladder Cancer in a Diabetic Population, 6/7/2011, available in DARRTS) provided incidence rates and incidence rate ratios of bladder cancer among patients enrolled in the dapagliflozin Phase 2b and 3 clinical trials program. Data from the Surveillance, Epidemiology, and End Results (SEER) database were used as an external comparator to calculate a standardized incidence ratio (SIR). The review was shared with the sponsor as part of FDA's background package for the Endocrinologic and Metabolic Drugs Advisory Committee meeting on dapagliflozin, scheduled for July 19, 2011. The sponsor commented on the background package and noted that the review contained three more recently reported cases (two exposed to dapagliflozin and one exposed to control) that occurred in two ongoing clinical trials, D1690C00018 and D1690C00019, which were not included in the denominator of the original review. To update these calculations, the Division of Metabolism and Endocrinology Products (DMEP) requested from the sponsor age- and sex-specific exposure data for nineteen Phase 2b and 3 clinical trials, including D1690C00018 and D1690C00019. This document includes updated analyses with complete exposure information. For detailed methodology, please refer to the original review.

2 UPDATED EXPOSURE DATA

The sponsor provided updated exposure data for nineteen Phase 2b and 3 clinical trials, including the ongoing studies D1690C00018 and D1690C00019. Because treatment assignment in the latter two studies is still masked, follow-up time by exposure was estimated by the sponsor based on actual follow-up time, which was then equally assigned to the two treatment arms. Although differential follow-up would not have been captured by this approach, the impact of resulting differences in person-time would likely be small and is not of concern in this review.

Age was unknown for one control subject and this subject was not part of the analysis. The impact of excluding this subject will be minor because the subject only contributed 0.6 years of follow-up.

3 BLADDER CANCER IN CLINICAL TRIALS

At the time of the original review and this updated analysis, 10 subjects were reported as having been diagnosed with bladder cancer in the phase 2b and 3 clinical trials on dapagliflozin. Nine of these cases occurred in the active treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76. Total follow-up of male patients randomized to dapagliflozin was 3007.1 subject-years (Table 1). With nine cases of bladder cancer occurring in male subjects exposed to dapagliflozin during this time, this rate amounts to 299.3 (95% CI, 136.6 – 568.1) new cases per 100,000 subject-years. This compares to one case during 1696.6 subject-years in controls, or 58.9 (95% CI, 0.8 – 327.9) new cases in controls per 100,000

subject-years. The rate ratio comparing the incidence of bladder cancer between active treatment and controls was 5.08 (95% CI, 0.70 – 222.6), with a two-sided p-value of 0.15 (Fisher’s exact). These estimates are pooled summary estimates and do not take heterogeneity between clinical trials into account, including potential imbalances in active treatment versus control ratios.

4 STANDARDIZED INCIDENCE RATIOS

Based on SEER data, only three (3.03) cases of bladder cancer would be expected in the male dapagliflozin population (Table 1) at a rate of 100.6 new cases per 100,000 subject years. The SIR of observed versus expected cases in males exposed to dapagliflozin was 2.98 (95% CI, 1.36 – 5.65), p=0.008. Almost two cases (1.87) would be expected among controls, where only one case was observed.

Table 1. Expected cases of bladder cancer in the male clinical trial sample

Age at diagnosis	Males			
	Observed cases, dapagliflozin	Dapagliflozin, person-time, males	Projected incidence, diabetic population, based on SEER data*	Expected bladder cancer cases in dapagliflozin patients
<25	0	1.5	0.4	0.0000
25-29	0	16.8	0.7	0.0001
30-34	0	47.3	1.5	0.0007
35-39	0	90.5	3.2	0.0029
40-44	0	180.1	7.0	0.0126
45-49	1	317.9	15.6	0.0497
50-54	0	428	31.8	0.1362
55-59	1	603.8	63.8	0.3853
60-64	2	560.5	111.8	0.6264
65-69	3	431.6	183.1	0.7905
70-74	2	228.9	275.3	0.6301
75-79	0	80	372.5	0.2980
80-84	0	19.8	455.5	0.0902
85+	0	0.5	506.9	0.0025
sum	9	3007.2	--	3.03

*per 100,000 person-years

5 DISCUSSION

This review updated my previous analysis with corrected exposure information. Estimated incidence rates for bladder cancer in subjects exposed to dapagliflozin decreased from 402 per 100,000 subject-years in the previous analysis to 299 per 100,000 subject-years in the updated analysis as a consequence of the increased denominator. Rates for controls decreased from 101 per 100,000 subject-years to 59 per 100,000 subject-years in the updated analysis. The incidence rate ratio, however, increased from

3.98 to 5.08 in the updated analysis, with a p-value of 0.15. The SIR, which compared observed cases of bladder cancer in the dapagliflozin-exposed subjects to the age- and sex matched U.S. general population, adjusted for an increased risk of bladder cancer in the diabetic population, decreased from 4.39 to 2.99, while maintaining a highly significant p-value of 0.008.

Findings of this review should be viewed in the light of several limitations. Cancer rates in SEER reflect the U.S. general population, while most of the clinical trial subjects were enrolled outside of the U.S., and international studies on the epidemiology of bladder cancer often found lower rates compared to the U.S. Also, clinical trial populations are often highly pre-screened for certain co-morbidities, which may result in an underestimated cancer incidence. Nevertheless, both limitations would result in a lower case count and therefore, the risk of bladder cancer associated with exposure to dapagliflozin would be underestimated. On the other hand, increased surveillance in a clinical trial setting, together with urinary symptoms associated with dapagliflozin could increase case detection of bladder cancer and lead to higher estimates compared to the background population. Lastly, it should be considered that the literature-based factor to adjust SEER estimates for a diabetic population is subject to uncertainty.

To summarize, the clinical trials were not powered to statistically distinguish between nine cases of bladder cancer in the active treatment arms compared to one case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Limitations suggest that comparisons between clinical trial data and a reference population should be carefully interpreted.

Christian Hampp, PhD

cc: EganA/ParksM/DunnS/IronyI/BishaiJ/MehreenH/DMEP
HamppC/JuJ/WysowskiD/IyasuS/TossaM/Dal PanG/OSE

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/s/

CHRISTIAN HAMPP
07/20/2011

SOLOMON IYASU
07/20/2011

**Memorandum of Consultation
Consult Tracking # 248-2011**

To: Mehreen Hai, Ph.D., RPM, DMEP
Somya Dunn, M.D., DMEP

Through: Scott Monroe, M.D. Division Director, DRUP
Theresa Kehoe, M.D., Team Leader, DRUP

From: Marcea Whitaker, M.D., Medical Officer, DRUP

Date: **July 18, 2011**

Re: **NDA 202293 Dapagliflozin
Treatment of Type II Diabetes
Bone effects**

Related IND: **IND 68,652**

Executive Summary: The effects of dapagliflozin on bone metabolism are not well-defined. The overall fracture rate was low (1.4%) and balanced between dapagliflozin and control groups. The apparent increased fracture rate in the moderate renal dysfunction population study (MB102029) was not demonstrated when all subjects (Phase 2b and Phase 3) with moderate renal dysfunction were pooled. These fracture events were also associated with various risks for falls (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state) or suffered significant trauma. It is well recognized that propensity to fall is a risk factor for fracture which is independent of bone mineral density. In addition, while a direct connection to the fracture events was not documented, rates of hypoglycemia, hypotension, dizziness, syncope, and falls were higher in this population. The 2-fold increase in fractures in patients with normal renal function over long term-exposure was associated with negligible laboratory changes suggesting that this imbalance may also not be significant. However, additional long-term data may provide further insight into this finding. In addition, there were minimal effects on mean bone mineral density (BMD) overall despite outliers with both positive and negative changes of approximately 8-12%. Bone biomarkers showed small inconsistent changes in bone resorption and bone formation. No clinically significant changes were seen in other laboratory values, including calcium, 25-OH vitamin D, magnesium, phosphorus and PTH (beyond what would be expected for the degree of renal dysfunction in the moderate renal dysfunction study).

Due to the cross-reactivity of dapagliflozin at sodium-dependent glucose cotransporter 2 (SGLT-2) sites, potential effects at SGLT-1 were investigated to determine if the increased fracture rates could be attributable to off-target effects and not related to bone metabolism. When evaluated, no imbalances were seen in off-target SGLT-1 sites, i.e. gastrointestinal and cardiac organ systems, at the clinical level. This may be due to the high specificity of dapagliflozin for SGLT-2 (approximately 1600-fold).

From the data reviewed, there is no indication that dapagliflozin exerts a clinically significant effect on bone loss or fracture. Full review of the 2-year data would be reassuring but generally would not be required for approval from a bone standpoint. While bone loss due to weight loss is a primary concern, further surveillance of bone formation/hyperostosis based on nonclinical evidence of vascular tissue mineralization, and increased bone resorption should also be monitored. We note that Study D1690C00012 is ongoing and data from 102 weeks of exposure will be provided when available.

Additional Internal Comments:

1. Actual change in BMD rather than change in T-score should be the measure of bone loss in clinical trials. A cut-off of >7% from baseline at lumbar spine or total hip at any post-baseline measurement is usually the criterion for drug discontinuation.

Addendum: In the June 16, 2011, submission, the sponsor clarified that the inclusion criterion in the 24-week CSR was reported incorrectly. The criteria should read “a decrease in BMD at DXA (T score \leq -2.5 or \geq **5% decrease in BMD**) at lumbar spine, femoral neck, or total hip from baseline.” This has been corrected in the 50 week study report and is acceptable.

2. If approved, a post marketing commitment assessing long-term BMD and fractures should be considered.
3. If a pediatric indication is sought, caution should be used when administering dapagliflozin in patients with open epiphyseal plates due to the risk of periarticular calcification.
4. The response to the May 31, 2011, Information Request for updated narratives based on T-score change remains outstanding.

Addendum: The narratives were received June 16, 2011 and are acceptable.

Consult Request:

DMEP is currently evaluating NDA 202293 for dapagliflozin (submitted 12/7/2010 by Bristol-Myers Squibb Company), which if approved, would be first-in-class for the treatment of Type 2 Diabetes. The applicant plans to market two doses, 10 mg (the standard dose) and 5 mg (for patients at risk for volume depletion due to diuresis) which would be taken once daily at anytime of the day regardless of meals.

The Division of Metabolic and Endocrine Products (DMEP) has expressed concern about imbalances in fractures following dapagliflozin exposure in 1) patients with normal renal function; and 2) patients in the moderate renal impairment study; as well as laboratory (PTH, phosphorus and magnesium) and bone biomarker changes.

DMEP has requested DRUP assess the risk for bone health and fracture based on:

- Bone laboratory and fracture data presented in the Summary of Clinical Safety (SCS) and SCS Appendices

- Bone biomarker data
- The 4-month safety update including DEXA results (4/28/11)

Background: In July, 2010, in response to a prior consult, DRUP reviewed a Phase 3, 24-week study protocol with a 78-week extension period (Study D1690C00012) to evaluate the effect of dapagliflozin in combination with metformin on body weight in Type 2 Diabetes Mellitus. The purpose of the consult was to assess the adequacy of the proposed bone biomarkers and biomarker endpoints.

Dapagliflozin is a reversible inhibitor of SGLT2 (sodium-dependent glucose cotransporter 2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose by inhibiting renal reabsorption of glucose, and by promoting urinary glucose excretion. Urinary glucose excretion induced by dapagliflozin depends on the amount of glucose filtered by the kidney. The filtered load is the product of the plasma glucose concentration and the GFR. Therefore, the action of the dapagliflozin is dependent upon the patient's baseline glycemic control and renal function, and is independent of beta cell function or insulin sensitivity.

The efficacy of dapagliflozin (glucose-lowering) is dependent on renal function and the drug should not be used in patients with moderate to severe renal impairment (eGFR <45 [MDRD] or CrCl <60 mL/min by Cockcroft-Gault). For patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose of may be appropriate.

SGLT2, found in the nephron proximal tubule, accounts for 90% of glucose reabsorption, while SGLT1, found in the nephron, as well as, in the small intestine mucosa, and heart, accounts for the remaining 10%. Both SGLTs are known as symporters as both sodium and glucose are transported in the same direction across the membrane.

Non-clinical overview: Vascular tissue mineralization and increased bone formation

In the preclinical studies, there were bone-related findings of concern, namely, vascular tissue mineralization and increased bone formation. In the 1, 3 and 6-month rat studies, vascular tissue mineralization and increased bone formation were noted at high exposure multiples ($\geq 2116 \times$ maximum recommended human dose [MRHD]). This was associated with increases in serum calcium despite increased urinary excretion of calcium. Increased bone formation was also noted in the sternum and femur. These bone changes were accompanied by an increase in bone mass and strength. Minimal to moderate vascular mineralization in multiple tissues and organs were also noted at high exposure multiples ($\geq 2116 \times$ exposures at the MRHD).

Similar findings occurred in preclinical studies in the same class of drug, canagliflozin, which is currently in the IND phase. Following administration of canagliflozin, there was a dose-dependent increase in sternum, femur/tibia trabecular bone hyperostosis (defined as an increase in trabecular bone) in rats. There was a decrease in trabecular separation (a measure of trabecular microstructure) of proximal tibia in male rats. At higher doses, a

decrease in femur bone area and mineral content (whole femur in males and proximal femur in females) were seen in both sexes in rats.

Reviewer’s comment: The sponsor of canagliflozin (Johnson and Johnson) suggested that hyperostosis was consistent with the dysregulation of calcium homeostasis due to an off-target inhibitory effect on SGLT1, leading to an increased absorption of calcium from the GI tract rather than from mobilization of calcium from bone. (From Investigator’s Brochure, canagliflozin). Based on data in the literature, one mechanism of calcium dysregulation could be increased active transport of calcium (via TRPV6) in the gut by a high luminal glucose concentration.

Bone and calcium markers such as 1,25 dihydroxyvitamin D, osteocalcin (a marker of bone formation), calcitonin, crosslinked C-telopeptide type 1 collagen (a marker of bone resorption) and PTH were generally reduced or unchanged in one or both sexes in rats. In male dogs, canagliflozin reduced bone mineral density of whole femur. There was also a decrease in 1,25 dihydroxyvitamin D and urinary deoxypyridinoline (bone resorption). See **Table 1**.

Table 1: Summary of available nonclinical and clinical data from SGLT2 inhibitors

	J &J	Bristol-Myers dapagliflozin
Rats	hyperostosis	hyperostosis
	↓ CTX, ↓DPD	↓ 1,25OHvitD, ↓ DPD
	↓ OC	
Dogs	---	↓ 1,25OHvitD, ↓ DPD
Humans- 12 week	↑ CTX	↑CTX, ↑DPD
		↑PTH

Reviewer’s comment: Inconsistent results were seen between the nonclinical and clinical studies. Nonclinical studies showed decreased bone turnover, while clinical studies suggested increased bone resorption and elevated PTH. Dapagliflozin data for change in CTX in rats was not available.

Review:

The short-term placebo controlled pool consists of two phase 2b studies and 10 phase 3 studies. The phase 2b studies were 12 weeks in duration while the phase 3 studies were 24 weeks in duration. The short plus long-term pool (24 weeks plus an extension phase) consisted of five Phase 3 studies. Five Phase 3 studies included 24 to 78-week extensions (maximum exposure 102 weeks). See **Table 2**.

Table 2: Overview of Placebo-controlled Clinical Studies: Short term and/or Long-term

Study number	N (Randomized/ completed)	Duration	Population	Drug groups
MB102008	390	12 weeks	T2DM Tx naïve	PLA/Dapa/Metformin
MB102009	71	12 weeks	Insulin-dependent T2DM	PLA/Dapa
MB102013	485	24 weeks	T2DM Tx naïve	PLA/Dapa
Long term	485/ 244	99-102 wks (2.1 yrs)	T2DM Tx naïve	PLA/Dapa
MB102014	546/483	24 wks	T2DM on metformin	PLA/Dapa
Long-term	546/339	102 wks (2.1yrs)	T2DM on metformin	PLA/Dapa
MB102029	252/162	102 wks	T2DM Moderate renal impairment	PLA/Dapa
Long-term				
MB102030	420/367	24 wks	T2DM on pioglitazone	PLA/Dapa
Long-term	420/339	48 weeks	T2DM on pioglitazone	PLA/Dapa
MB102032	282/262	24 wks	T2DM Tx naïve	PLA/Dapa
D1690C00005	597/546	24 wks	T2DM on sulfonylurea	PLA/Dapa
Long-term	597/519	48 wks	T2DM on sulfonylurea	PLA/Dapa
D1690C00006	808/711	24 wks	Insulin-dependent T2DM	PLA/Dapa
Long-term	808/676	48 wks	Insulin-dependent T2DM	PLA/Dapa
Long-term	808/ongoing	104 wks (2.1 yrs)	Insulin-dependent T2DM	PLA/Dapa
D1690C00012 DXA Study	182/169	24 wks	T2DM on metformin	PLA/Dapa
D1692C00005	279/258	12 wks	T2DM, Japanese	PLA/Dapa

Reviewer’s comment: Overall fracture risk is higher at baseline for those with diabetes particularly in those with Type 1 diabetes and Type 2 insulin-dependent diabetes, as well as those taking thiazolidinediones for greater than 1 year (increased risk of 50%, Habib, et al. [2010]).

Patient population- Overall: The clinical program enrolled males and females ≥ 18 years of age. There was an equal percentage of males and females enrolled with a mean age of 56 years (21.3% were 65 or older and 2.8% were ≥ 75 years or older). Subjects had “uncontrolled diabetes” defined as HbA1c ranging from 7-10.5% (with some studies enrolling subjects with a HbA1c upper limit of 12%). Subjects with mild and moderate renal impairment were also included in the Phase 3 studies, although subjects with significant renal impairment were excluded. Mild renal impairment (60-90 ml/min) accounted for 51% of subjects and moderate renal impairment (30-60 ml/min) accounted for 11.8%. One study, MB102029, exclusively enrolled subjects with moderate renal impairment. Phase 3 studies did not exclude subjects with advanced stages of T2DM, such as those with chronic complications (retinopathy, neuropathy, mild nephropathy, or chronic CV disease). However, subjects with significant hepatic disease, unstable CV disease including Class III and IV heart failure were excluded.

Brief overview of Efficacy:

The clinical development program showed that dapagliflozin has consistent efficacy whether used as monotherapy or as add-on therapy. Following oral administration, the pharmacodynamic effect of glucosuria is detected within 1 hour post-dose and results in reductions in fasting glucose, post-prandial glucose and HbA1c. Clinically meaningful

reductions in HbA1c (0.4 – 0.7%) were observed with 10 mg dapagliflozin. The loss of calories due to persistent glucosuria resulted in reductions in body weight.

Overview of Safety:

Studies investigated dapagliflozin doses of 2.5 mg, 5 mg and 10 mg. The sponsor's analysis of safety was performed on the short-term double-blind data in the placebo-controlled pool and the short-term plus long-term data up to 102 weeks.

Imbalances in Adverse Events:

The following imbalances were noted in the clinical program:

- *Increased renal events in moderate renal impairment and in subjects over age 65*
Overall, there were no increased events of renal impairments or failure. However, events of renal impairment or failure were more common in subjects expected to have reduced glomerular filtration rate (GFR), such as subjects with moderate renal impairment at baseline and subjects over 65 years of age. In these subgroups, more AEs occurred in subjects treated with dapagliflozin than placebo.

- *Volume Depletion*
Events of hypotension/hypovolemia/dehydration (volume depletion) were slightly more common in subjects treated with dapagliflozin compared with placebo/control.

- *Bone Health*
Bone health was evaluated in the dapagliflozin clinical development program due to the possible effects of dapagliflozin on body weight, renal tubular handling of calcium and phosphorus, metabolism of vitamin D, and the risk of fractures associated with TZDs used as rescue therapy in some dapagliflozin studies. Fractures were reported in both the dapagliflozin and control groups at similar rates. Imbalances in fracture rates were seen in the single study enrolling diabetic subjects with moderate renal impairment (MB102029), however, this imbalance was not seen when subjects with moderate renal impairment were pooled across all Phase 2b and Phase 3 studies.

1. Fractures

The primary safety patient population discussed in this review refers to the placebo-controlled pool comprising 12 studies including 12 week Phase 2b studies and 24 week data from all Phase 3 studies, with five studies contributing long-term data. For some analyses, sponsor data pooled from all phase 2b and 3 studies, including short-term plus long-term data from all 14 studies, are reported.

Overall placebo-controlled population (Placebo-controlled pool, DAP n=3291, Placebo n=1393)

Short-term studies: Overall, in the short-term placebo-controlled pooled cohort (up to 24 weeks exposure), fractures were reported in <1% of subjects. See **Table 3**, sponsor Table 77. There were 24 total fractures reported with a greater percentage of fractures occurring in the placebo group, 0.7%, than in the dapagliflozin group, 0.4%.

Table 3: Sponsor's Table 77

Table 77: Adverse Events of Fracture Short-term Double-blind Treatment Period Including Data After Rescue Placebo-controlled Pool Treated Subjects

Preferred Term (%)	PLA N = 1393	DAPA 2.5MG N = 814	DAPA 5MG N = 1145	DAPA 10MG N = 1193	DAPA TOTAL N = 3291
TOTAL SUBJECTS WITH AN EVENT	10 (0.7)	1 (0.1)	7 (0.6)	6 (0.5)	14 (0.4)
ANKLE FRACTURE	2 (0.1)	0	2 (0.2)	2 (0.2)	4 (0.1)
FOOT FRACTURE	1 (0.1)	0	1 (0.1)	2 (0.2)	3 (0.1)
FACIAL BONES FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
HIP FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
SPINAL COMPRESSION FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
BONE FISSURE	0	0	1 (0.1)	0	1 (<0.1)
FEMORAL NECK FRACTURE	1 (0.1)	0	0	0	0
HAND FRACTURE	1 (0.1)	0	2 (0.2)	0	2 (0.1)
RADIUS FRACTURE	2 (0.1)	0	0	0	0
RIB FRACTURE	1 (0.1)	0	0	0	0
TIBIA FRACTURE	1 (0.1)	0	1 (0.1)	0	1 (<0.1)
TRAUMATIC FRACTURE	0	1 (0.1)	0	0	1 (<0.1)
UPPER LIMB FRACTURE	1 (0.1)	0	0	0	0

Appears this way on original

Short-term + Long-term studies: In the short- plus long-term studies (up to 50 weeks), there was an equal rate of fractures (1.4%) in the dapagliflozin and placebo groups. See **Table 4**, sponsor Table 78. About two-thirds (26 of 38 or 68%) of the reported fractures were considered fragility (osteoporotic) fractures based on location (ankle, hip, humerus, vertebral, limb, rib, wrist) although the rate of fragility fractures was lower in the dapagliflozin group compared to placebo (0.88% vs. 1.0%). [Bone fissure has been subsequently excluded from the fracture events by the sponsor.]

Table 4: Sponsor's Table 78

Table 78: Adverse Event Summary Adverse Events of Fracture Short-term plus Long-term Treatment Period Including Data After Rescue Placebo-controlled Pool Treated Subjects

Preferred Term (%)	PLA N = 624	DAPA 2.5MG N = 625	DAPA 5MG N = 767	DAPA 10MG N = 768	DAPA TOTAL N = 3160
TOTAL SUBJECTS WITH AN EVENT	10 (1.4)	7 (1.1)	12 (1.6)	11 (1.4)	30 (1.4)
ANKLE FRACTURE	2 (0.3)	2 (0.2)	2 (0.2)	3 (0.4)	6 (0.3)
FOOT FRACTURE	1 (0.1)	0	2 (0.3)	3 (0.4)	5 (0.2)
HIP FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
HUMERUS FRACTURE	1 (0.1)	0	0	1 (0.1)	1 (<0.1)
OPEN FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
SPINAL COMPRESSION FRACTURE	0	0	0	1 (0.1)	1 (<0.1)
TRAUMATIC FRACTURE	0	1 (0.2)	1 (0.1)	1 (0.1)	3 (0.1)
BONE FISSURE	0	0	2 (0.3)	0	2 (0.1)
FACIAL BONES FRACTURE	0	1 (0.2)	1 (0.1)	0	2 (0.1)
FEMORAL NECK FRACTURE	1 (0.1)	0	0	0	0
HAND FRACTURE	1 (0.1)	0	3 (0.4)	0	3 (0.1)
LOWER LIMB FRACTURE	0	1 (0.2)	0	0	1 (<0.1)
LUMBAR VERTEBRAL FRACTURE	1 (0.1)	0	0	0	0
MULTIPLE FRACTURES	0	1 (0.2)	0	0	1 (<0.1)
PATELLA FRACTURE	1 (0.1)	0	0	0	0
RADIUS FRACTURE	1 (0.1)	0	0	0	0
RIB FRACTURE	1 (0.1)	1 (0.2)	0	0	1 (<0.1)
TIBIA FRACTURE	0	0	1 (0.1)	0	1 (<0.1)
UPPER LIMB FRACTURE	0	2 (0.3)	0	0	2 (0.1)
WRIST FRACTURE	0	0	1 (0.1)	0	1 (<0.1)

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Reviewer's comment: About 1/3 of fractures were non-fragility type fractures. Of fragility fractures, there were lower rates of fractures occurring in the dapagliflozin

group (0.88% vs 1.0%) suggesting no increase in osteoporotic fracture above baseline.

Compared to the 40 fractures reported in the original NDA, 44 fracture events were reported in the 4MSU ISS, 32 (1.4%) in events in the dapagliflozin groups [pooled] and 12 (1.5%) in the placebo group (see **Table 5**, sponsor Table 18).

Table 5: Sponsor’s Table 18

Table 18: Fractures in the Phase 2b and 3 Clinical Program: Short-term plus Long-term 4-Month Safety Update Data

	Number (%) of Subjects			
	N	AEs	SAEs	AEs Leading to Discontinuation
All Phase 2b and 3 Pool				
Dapagliflozin Total	4310	56 (1.3) ^a	8 (0.2)	2 (< 0.1)
All Control	1962	25 (1.3)	10 (0.5)	1 (<0.1)
Placebo-controlled Pool				
2.5 mg Dapagliflozin	625	9 (1.4)	0	1 (0.3)
5 mg Dapagliflozin	767	12 (1.6) ^a	1 (0.1)	1 (0.1)
10 mg Dapagliflozin	859	11 (1.3)	5 (0.6)	0
Placebo	785	12 (1.5)	5 (0.6)	0

To determine the number of subjects at risk for osteoporosis based on age (i.e., postmenopausal), the reviewer queried the adverse event dataset (“ADAE”) from the 4MSU for “fracture” from the placebo-controlled studies resulting in 69 events in 66 subjects. [Note: It is unclear why there are more events in the dataset than reported in the ISS.] In the placebo group (see **Table 6**), there were 18 total fracture events with 13 of these events occurring in women. Of all women (age range 37-82 years), only two women were not in the postmenopausal age range (defined as age ≥52 years). One fracture occurred prior to the study start. Five remaining events occurred in men ages 37, 57, 58, 65, and 69.

Reviewer’s comment: Menopausal status was not captured in the demographic dataset.

Table 6: Placebo group fractures listed by age (women only)

USUBJID	SEX	RACE	AGE	TRTCD	AEDECOD	AESTDY	AETERM
D1690C00006-1202-8	F	WHITE	37	PLA + INS	FOOT FRACTURE	729	broken right little toe
MB102032-69-310	F	ASIAN	45	PLA	ANKLE FRACTURE	153	FRACTURE TALUS
MB102014-94-371	F	WHITE	53	PLA + MET	RADIUS FRACTURE	95	RIGHT RADIUS FRACTURE
D1690C00012-304-25	F	WHITE	56	PLA + MET	ULNA FRACTURE	357	Right ulnar fracture
D1692C00005-6-1	F	ASIAN	59	Placebo	HAND FRACTURE	-26	Fracture(Distal phalanx of right first finger)
D1690C00006-1906-1	F	WHITE	61	PLA + INS	ANKLE FRACTURE	59	triple compound fracture with dislocation on the right ankle
MB102013-19-768	F	WHITE	62	PLA	FEMORAL NECK FRACTURE	145	FRACTURE LEFT FEMORAL NECK
D1690C00005-1018-1	F	WHITE	62	PLA + GLI	PATELLA FRACTURE	294	fracture of right kneecap
MB102032-82-286	F	WHITE	65	PLA	ANKLE FRACTURE	23	CLOSED MEDIAL MALLEOLAR FRACTURE OF RIGHT LOWER EXTREMITY
D1690C00006-1304-16	F	WHITE	65	PLA + INS	ANKLE FRACTURE	517	Left ankle fracture
D1690C00006-1703-11	F	WHITE	68	PLA + INS	FOOT FRACTURE	75	RIGHT HALUX PROXIMAL PHALANX FRACTURE
MB102032-77-283	F	WHITE	70	PLA	RADIUS FRACTURE	23	CLOSED FRAGMENTAL FRACTURE OF RIGHT RADIUS IN TYPICAL PLACE WITH SHIFT
MB102029-35-68	F	WHITE	82	PLA	SPINAL COMPRESSION FRACTURE	559	T12 COMPRESSION FRACTURE

In comparison, there were 50 events in the dapagliflozin groups. There were 24 events in 23 women (see **Table 7**). Of all women (age range 26-82 years), 4 were not in the postmenopausal age range. The remaining 27 events (occurring in 25 men) included the following age categories: ≤ 50 yrs (n=7), 50-70 yrs (n=26), and >70 (n=0).

Table 7: Dapagliflozin fractures listed by age (women only)

USUBIID	SEX	RACE	AGE	TRTCD	AEDECOD	AESTDY	AELLT
MB102013-94-532	F	WHITE	32	DAPA 10MG (QAM-GRP2)	ANKLE FRACTURE	199	ANKLE FRACTURE
MB102014-44-189	F	OTHER	47	DAPA 2.5MG + MET	LOWER LIMB FRACTURE	375	LEG FRACTURE
MB102014-44-189	F	OTHER	47	DAPA 2.5MG + MET	UPPER LIMB FRACTURE	375	ELBOW FRACTURE
MB102013-8-62	F	WHITE	51	DAPA 10MG (QAM)	ANKLE FRACTURE	352	ANKLE FRACTURE
MB102030-26-187	F	WHITE	52	DAPA 5MG + PIO	FOOT FRACTURE	98	FOOT FRACTURE
D1690C00006-1309-5	F	WHITE	54	DAPA 5MG + INS	ANKLE FRACTURE	9	ANKLE FRACTURE
D1690C00006-1211-7	F	WHITE	58	DAPA 10MG + INS	ANKLE FRACTURE	35	BROKEN ANKLE
D1690C00006-1005-4	F	WHITE	58	DAPA 10MG + INS	FOOT FRACTURE	223	FRACTURED METATARSAL
D1690C00006-1502-1	F	WHITE	58	DAPA 10MG + INS	HUMERUS FRACTURE	550	FRACTURE OF HUMERUS
D1690C00006-1808-5	F	WHITE	60	DAPA 2.5MG + INS	RADIUS FRACTURE	520	RADIUS FRACTURE
MB102029-35-138	F	WHITE	61	DAPA 5MG	FOOT FRACTURE	108	FRACTURED METATARSAL
MB102014-54-149	F	WHITE	62	DAPA 5MG + MET	WRIST FRACTURE	527	WRIST FRACTURE
D1692C00005-4-1	F	ASIAN	63	DAPA 5MG	ANKLE FRACTURE	17	MALLEOLAR FRACTURE
MB102029-59-140	F	WHITE	64	DAPA 10 MG	UPPER LIMB FRACTURE	292	ELBOW FRACTURE
D1692C00005-10-4	F	ASIAN	65	DAPA 1 MG	SPINAL COMPRESSION FRACTURE	42	FRACTURED VERTEBRA (COMPRESSION)
MB102013-96-564	F	WHITE	65	DAPA 2.5MG (QPM)	RIB FRACTURE	315	RIB FRACTURE
D1690C00006-1812-12	F	WHITE	69	DAPA 10MG + INS	SPINAL COMPRESSION FRACTURE	63	COMPRESSION OF FRACTURED VERTEBRA
D1690C00006-1203-1	F	WHITE	69	DAPA 2.5MG + INS	MULTIPLE FRACTURES	587	MULTIPLE FRACTURES
MB102029-126-317	F	BLACK	69	DAPA 5MG	FOOT FRACTURE	179	FOOT FRACTURE
D1690C00006-1701-1	F	WHITE	70	DAPA 5MG + INS	TIBIA FRACTURE	16	TIBIA FRACTURE
MB102029-49-454	F	WHITE	74	DAPA 10 MG	TRAUMATIC FRACTURE	52	TRAUMATIC FRACTURE
D1690C00006-1003-18	F	WHITE	75	DAPA 5MG + INS	FOOT FRACTURE	324	FOOT FRACTURE
MB102029-11-102	F	WHITE	80	DAPA 10 MG	WRIST FRACTURE	217	WRIST FRACTURE
MB102029-11-21	F	WHITE	82	DAPA 10 MG	HIP FRACTURE	586	HIP FRACTURE

Reviewer’s comment: The majority of fractures (mostly fragility fractures) occurred in women who were in the postmenopausal age range. However, menopausal status was not captured in the dataset.

Moderate Renal Dysfunction Study (MB102029)

Study MB102029 was the only study performed in diabetic subjects with moderate renal impairment. Adverse events of fracture in this study were more common in subjects treated with dapagliflozin compared with placebo. Poorly controlled diabetic subjects were randomized to dapagliflozin 5, 10, or placebo. Open-label rescue was permitted. Subjects received randomized treatment for 24 weeks plus 28 weeks extension plus a

52-week blinded long-term extension period (up to 102 weeks). Subjects were at least 18 years of age, had T2DM, moderate renal impairment (30-59 mL/min), inadequate glycemic control (defined as HbA1c \geq 7.0% and \leq 11.0%), and BMI \leq 45.0.

Cumulative fracture rates during each phase of the study are shown in the following tables (**Table 8** and **Table 9**). A combined rate of 1.8% was seen after 24 weeks of exposure (data not shown).

However, at the end of 52 weeks and 102 weeks, a significant imbalance in fractures (6.0% at 52 weeks and 7.1% at 102 weeks) was seen in the dapagliflozin groups combined compared to placebo (0%). A dose-response relationship was also demonstrated.

Table 8: MB102029 after 52 weeks of exposure (fractures)

Preferred Term (%)	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL SUBJECTS WITH AN EVENT	0	3 (3.6)	7 (8.2)
FOOT FRACTURE	0	2 (2.4)	1 (1.2)
LUMBAR VERTEBRAL FRACTURE	0	0	1 (1.2)
PATELLA FRACTURE	0	0	1 (1.2)
RADIUS FRACTURE	0	0	1 (1.2)
TRAUMATIC FRACTURE	0	0	1 (1.2)
UPPER LIMB FRACTURE	0	0	1 (1.2)
WRIST FRACTURE	0	0	1 (1.2)
HUMERUS FRACTURE	0	1 (1.2)	0

Source: CSR MB102029, Table 8.6.6.2

Table 9: MB102029 after 102 weeks of exposure (fractures)

Preferred Term (%)	Placebo N=84	DAPA 5MG N=83	DAPA 10MG N=85
TOTAL SUBJECTS WITH AN EVENT	0	4 (4.8)	8 (9.4)
FOOT FRACTURE	0	3 (3.6)	1 (1.2)
HIP FRACTURE	0	0	1 (1.2)
LUMBAR VERTEBRAL FRACTURE	0	0	1 (1.2)
PATELLA FRACTURE	0	0	1 (1.2)
RADIUS FRACTURE	0	0	1 (1.2)
TRAUMATIC FRACTURE	0	0	1 (1.2)
UPPER LIMB FRACTURE	0	0	1 (1.2)
WRIST FRACTURE	0	0	1 (1.2)
HUMERUS FRACTURE	0	1 (1.2)	0

Source: 4-month Safety Update, Table 7.6.6, p.59/2637

Most (70%) of the fractures occurred during the time period between weeks 24 and 52. The sponsor reports that no subject in the placebo group had a reported fracture during this 52-week period. (However, the dataset does show that one placebo subject did have a vertebral fracture following a syncopal episode but this occurred at Day 559 (approximately Week 77). See reviewer's comment below). There was no apparent pattern with respect to the site of fracture, or with reported occurrences of hypotension or hypoglycemia. Hypoglycemia was reported in at least one narrative. All fractures were assessed as mild or moderate in intensity and did not lead to discontinuation. After 52 weeks, two subjects had a fall or trauma, and the sponsor reports 6 of 10 subjects with either diabetic neuropathy or orthostatic hypotension at either baseline or during the treatment. None had a history of osteoporosis. Cumulative narratives are presented below.

Cumulative Fracture Narratives (12 events after 102 weeks of exposure):

Dapagliflozin 5 mg

- Subject MB102029-35-138: A 61-year-old female (dapagliflozin 5 mg group) with bilateral osteoarthritis of the feet who sustained a fracture of the foot bone (second metatarsal bone) after hitting a chair.
- Subject MB102029-37-238 (67-year-old male, dapagliflozin 5 mg group) with history of osteoarthritis of the feet suffered a foot fracture after tripping over a hose.
- Subject MB102029-85-371: A 67-year-old male, dapagliflozin 5 mg group, with history of osteoarthritis who slipped on ice and had a left humerus fracture.
- Subject MB102029-126-317: A 69-year-old female, dapagliflozin 5 mg group, with history of arthritis who had a left foot fracture following a fall while getting off a bus.

Dapagliflozin 10 mg

- Subject MB102029-4-232: A 69-year-old male, dapagliflozin 10 mg group, with peripheral vascular disease tripped over a tree root and suffered a fracture (left radial head).
- Subject MB102029-11-21 An 82-years-old female; dapagliflozin 10 mg group, had a fall on Day 586 and experienced a right hip fracture. No syncope or hypoglycemia was confirmed. The subject had degenerative arthritis of the hip. The subject had experienced a previous AE of fall at Day 366, blood pressure and glucose were not obtained.
- Subject MB102029-11-102 : An 80-year-old female; dapagliflozin 10 mg group, s/p total hip replacement who fell from a standing height while starting to use her walker and experienced a left wrist fracture.
- Subject MB102029-25-246: A 59-year-old male (dapagliflozin 10 mg group) with history of diabetic neuropathy with the lumbar vertebral fracture sustained following a trucking accident (collapse of road at shipping yard).
- Subject MB102029-49-454: A 74-year-old female, dapagliflozin 10 mg group) experienced a fracture (right wrist) after falling.
- Subject MB102029-59-140: A 64-year-old female, (dapagliflozin 10 mg group) had a fall while fasting while walking and sustained an upper limb fracture (elbow). Blood glucose was not available
- Subject MB102029-61-483: A 55-year-old male, dapagliflozin 10 mg group) s/p foot amputation who stumbled over a power line and sustained a patella fracture;
- Subject MB102029-88-423: A 70-year-old male, dapagliflozin 10 mg group with diabetic neuropathy who was hit by a tractor and sustained a foot fracture (2nd right toe). Hypoglycemia was reported by in the study report but was not included in the narrative.

Placebo

During review of datasets and narratives, one fracture was noted to have occurred in the placebo group.

- Subject MB102029-35-68: An 82 year old Caucasian female with T2DM, HTN, CAD. Following a syncopal episode and fall on Study Day 559, she presented to the ER complaining of flank and low back pain. A T12 vertebral compression fracture was diagnosed.

Reviewer’s comments: The mean age was 68 years with equal sex distribution. More events occurred in the 10 mg group with one event occurring in the placebo group (not reported in the sponsor’s table). Per the sponsor, “all subjects with fractures experienced a fall or coincident trauma preceding the fracture” however, on closer review only 2 cases had significant trauma (hit by tractor, trucking accident); 5 cases had mild trauma (slipped on ice, tripped, hit chair, while getting off bus), one case involved a subject with foot amputation who tripped. Four cases had no trauma. Overall, seven of the 12 cases (58%) involved fragility type fractures with minimal trauma (female mean age=73, male mean age=68). Of note, this patient population was older than in the other Phase 3 placebo-controlled studies (mean age, 68 vs 56 years) and subjects had a longer mean duration of diabetes (16.9 years vs 1.4 to 8 years) [data from ISE, p. 67/214].

Negligible changes in laboratory values were noted. No conclusions can be made based on the presence or absence of fragility fractures between groups in this study based on the following:

- 1) Fractures generally occurred in subjects who were at risk for osteoporosis based on age. Only one study (D1690C00012) measured BMD and excluded subjects based on baseline T-score, therefore, some subjects in study MB102029 could have had osteoporosis at baseline.
- 2) Fracture events were associated with various risks for falls (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state) or sustained significant trauma. It is well-recognized that the propensity to fall is a risk factor for fracture which is independent of bone mineral density.

In light of no imbalance in fracture events seen in the overall patient population nor when all subjects with moderate renal dysfunction were pooled across studies (discussed below), the apparent imbalance does not appear to be significant. However, additional data may provide further insight.

Subgroups based on Renal Function:

The sponsor further evaluated the fracture imbalance in study MB102029 by analyzing pooled data across placebo-controlled studies based on baseline renal function (mild, moderate, normal). See **Table 10**.

Table 10: Fracture AEs by Baseline eGFR subgroups – Short +Long-term/52 weeks (pooled placebo-controlled)

GFR (ml/min)	Placebo	dapagliflozin 2.5 mg	dapagliflozin 5 mg	dapagliflozin 10 mg	dapagliflozin Total
≥30 and <60	2 (2.8%)	1 (1.4%)	2 (2.3%)	0	3 (1.3%)
≥60 and <90	7 (1.8%)	5 (1.4%)	6 (1.4%)	9 (2.2%)	20 (1.7%)
≥90	1 (0.4%)	1 (0.5%)	4 (1.7%)	2 (0.7%)	7 (1.0%)

Source: Appendix 319B, ISS, p. 11094/12312 (Original NDA submission)

- Moderate Renal Dysfunction (≥30 and <60 ml/min) (All Phase 2b/3 Studies):
When all subjects with moderate renal dysfunction were pooled, no increases

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compared to placebo in fractures were seen at 52 weeks (1.3% dapagliflozin vs 2.8 % placebo) which was different than results for MB102029.

- Mild Renal Dysfunction (≥ 60 and < 90 ml/min): No increases compared to placebo in fractures were seen in those with mild dysfunction (1.8% dapagliflozin vs 1.7%, placebo) after 52 weeks.
- Normal Renal function (≥ 90 ml/min): For subjects with normal baseline renal function, short-term studies (up to 6 months) showed a 3-fold rate increase in fractures in DAP groups (0.6 % compared to placebo 0.2%) (data not shown). After 52 weeks, a 2-fold increase was seen (1.0% compared to placebo 0.4%). See **Table 10**.

Reviewer's comment: The 2-fold increase in fractures in patients with normal renal function in the long-term studies is difficult to explain from a mechanistic perspective. There were negligible laboratory changes associated with this finding. Additional long-term data may be able to shed additional light on this finding.

There were no reported changes in calcium, phosphate, 25-OH vitamin overall. Small increases in PTH were noted.

Note: Separate laboratory reports for GFR categories ≥ 90 or between ≥ 60 and < 90 were not reported.

Subset of Moderate Renal Dysfunction (45-60 ml/min)

The sponsor further analyzed the subset of pooled moderate renal dysfunction falling between a GFR of 45-60 ml/min. This categorization was chosen based on both the NDDK criteria (category 3A) and because most subjects with moderate renal dysfunction in the placebo-controlled pool (including MB102029), had baseline eGFR between 45 and 60 ml/min. Within the 3A category, the dapagliflozin group was compared to the placebo group. The following events were more frequent ($\geq 2\%$) in the dapagliflozin groups: 1) events of renal impairment, 2) increases in PTH (without evidence of increased fractures), 3) and events of hypotension.

Table 11: AE listing for 3A population and GFR 45-60 ml/min – Short + Long-term

	Dapa total (n=267)	Placebo (n=104)
Adverse Event		
Fractures -all	4 (1.5%)	1 (1%)
Lumbar vertebral	1 (0.4%)	0
Radius Fx	1 (0.4%)	0
Foot Fx	2 (0.7%)	1 (1%)
Humerus Fx	0	1 (1.0%)
Hypoglycemia	1 (0.4%)	0
Hypotension	8 (3%)	1 (1%)
Blood pressure/blood pressure systolic decreased	1 (0.4%)	1 (1%)
Syncope	2 (0.7%)	1 (1%)
Postural dizziness	1 (0.4%)	0
Dizziness	13 (4.9%)	5 (4.8%)
Orthostatic hypotension	3 (1.1%)	0
Any hypotension/postural dizziness/orthostatic hypotension/syncope	28 (10.4%)	8 (7.7%)
Falls	6 (2.2%)	2 (1.9%)

Source: Appendix 89L, ISS Appendices p. 2106/12312

Reviewer’s comment:

In the moderate renal dysfunction population, fractures were uncommon but occurred more frequently in the dapagliflozin group, 1.5% vs 1%, accounting for five total fractures. There was an increase in events of hypotension, dizziness or syncope combined (10.4% dapagliflozin vs 7.7% placebo) and a slight increase in falls (2.2% vs 1.9%) in this population (see Table 11). “Events of “orthostatic hypotension” appeared dose-related while events of “hypotension” did not. The increased incidence of hypotension overall suggest that the occurrence of fracture in the moderate renal dysfunction population could be related to blood pressure changes and subsequent injury, i.e. falls, and may not be related to changes in bone integrity. This finding may account for more events occurring in study MB102029 as these patients had longer duration of diabetes and would be at increased risk of autonomic neuropathy, in addition to peripheral neuropathy. Negligible changes in laboratory values were also noted. Overall, the apparent imbalances in fractures do not appear to be significant.

2. Laboratory Changes

Serum calcium: No significant changes in mean serum calcium were noted up to Week 102 in the placebo-controlled pool.

25OH Vitamin D: No significant changes in mean vitamin D were noted up to Week 102 in the placebo-controlled pool.

Serum Phosphorus (normal range 2.4 - 4.1 mg/dl): The mean PO₄ concentrations remained within normal limits through Week 102. The mean change from baseline to Week 24 (0.12 [dapa] vs 0 [placebo]) and Week 102, (0.05 [dapa] vs 0.10 [placebo]) were small. (See **Table 12**). These changes were not clinically significant.

Table 12: Inorganic Phosphorus (mg/dL): Summary statistics for Inorganic phosphorus for Short + Long-term period (placebo-controlled pool)

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
ST Treatment SCS WK 24	PLA	598	3.59	0.523	0	0.0204
	Dapa 2.5mg	554	3.63	0.506	0.9	0.0214
	Dapa 5mg	668	3.71	0.507	0.12	0.0201
	Dapa 10 mg	676	3.73	0.520	0.14	0.0192
	Dapa total	1898	3.69	0.513	0.12	0.0117
LT Treatment SCS WK 102	PLA	107	3.71	0.673	0.10	0.0656
	Dapa 2.5mg	136	3.65	0.454	0.04	0.0403
	Dapa 5mg	159	3.58	0.489	0.04	0.0390
	Dapa 10 mg	166	3.70	0.499	0.06	0.0384
	Dapa total	461	3.64	0.484	0.05	0.0226

Source: Appendix 67B ISS

Magnesium (normal range 1.5 – 2.5 mEq/L): Mean magnesium values remained in normal range in the placebo-controlled pool. Small changes from baseline in mean serum magnesium levels was reported at Week 24 in the dapagliflozin (0.05 – 0.09 mEq/L) and placebo (-0.01 mEq/L). At Week 102, the mean change from baseline in the dapagliflozin groups ranged from -0.07 to -0.10 mEq/L, compared with -0.16 mEq/L in the placebo group. These changes are not clinically significant. See **Table 13**.

Table 13: Magnesium (mEq/L): Summary statistics for Short + Long-term Period (placebo-controlled pool)

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
ST Treatment SCS WK 24	PLA	598	1.69	0.187	-0.01	0.0085
	Dapa 2.5mg	555	1.75	0.203	0.05	0.0100
	Dapa 5mg	668	1.77	0.217	0.09	0.0087
	Dapa 10 mg	676	1.79	0.179	0.08	0.0098
	Dapa total	1899	1.77	0.200	0.07	0.0055
LT Treatment SCS WK 102	PLA	107	1.61	0.149	-0.16	0.0250
	Dapa 2.5mg	136	1.68	0.164	-0.09	0.0229
	Dapa 5mg	159	1.68	0.164	-0.07	0.0205
	Dapa 10 mg	165	1.71	0.130	-0.10	0.0240
	Dapa total	460	1.69	0.153	-0.08	0.0130

Source Appendix 69B

Intact PTH (normal range pg/ml 11-54 pg/mL): Small increases in mean change from baseline in PTH (intact) were seen in the dapagliflozin groups compared to placebo (2.4 vs 0.1 at 24 weeks and 2.1 vs -2.9 at 102 weeks). Overall, mean values remained within the normal range. See **Table 14**. These changes are not clinically significant.

Table 14: Intact PTH (pg/ml): Summary statistics for Short + Long-term Period (Placebo-controlled pool)

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
ST Treatment SCS WK 24	PLA	586	36.9	20.92	0.1	0.639
	Dapa 2.5mg	535	40.5	21.21	2.5	0.718
	Dapa 5mg	656	38.3	18.10	2.4	0.549
	Dapa 10 mg	656	39.6	21.95	2.3	0.713
	Dapa total	1847	39.4	20.45	2.4	0.381
LT Treatment SCS WK 102	PLA	102	35.3	17.77	-2.9	1.561
	Dapa 2.5mg	131	38.6	19.75	1.5	1.375
	Dapa 5mg	151	39.8	21.64	3.1	1.174
	Dapa 10 mg	158	37.9	18.74	1.6	1.068
	Dapa total	440	38.7	20.05	2.1	0.690

Source: appendix 59B

Greater increases in PTH were seen in the moderate renal failure study (MB102029) (see **Table 15**) where all treatment groups had an increase in PTH levels from baseline with a larger increase in each dapagliflozin group compared with placebo, particularly in the dapagliflozin 10 mg group at weeks 24 and 52. All subjects had elevated PTH at baseline (mean 66-70). At 24 weeks, the mean values ranged from 77-96 pg/ml in the dapa groups compared to 68 pg/ml in the placebo group (mean change from baseline of 4 and 26 pg/ml, for the 5 and 10 mg groups, respectively). At 104 weeks, the mean values ranged from 79-105 pg/ml, with mean change from baseline of 23 and 19 pg/ml, for the 5 and 10 mg groups, respectively. The changes were overall dose-dependent.

Table 15: Intact PTH (pg/ml): Study 102029 Short + Long-term Period

Period/Visit	Treatment Group	N	Mean	SD	Mean Change from baseline	SE
Lead-in Baseline	PLA	81	66.52	52.993		
	Dapa 5 mg	78	70.15	57.448		
	Dapa 10 mg	79	68.53	48.855		
ST Treatment WK 24	PLA	58	68.48	52.728	2.90	4.73
	Dapa 5 mg	64	77.22	67.553	4.05	5.25
	Dapa 10 mg	63	96.59	124.379	25.95	14.80
LT Treatment WK 52	PLA	45	62.49	43.994	1.13	4.61
	Dapa 5 mg	60	76.58	60.201	9.25	5.41
	Dapa 10 mg	60	84.10	54.828	11.93	5.15
LT Treatment WK 104	PLA	2	30.50	7.778	-4.00	11.00
	Dapa 5 mg	8	79.88	28.352	23.50	9.67
	Dapa 10 mg	10	105.70	64.515	19.20	5.77

Source: Appendix 7.36C

Reviewer's comment: Elevated baseline PTH levels are common in renal insufficiency. As vitamin D conversion is compromised, serum calcium decreases leading to increased levels of PTH, as well as increases in PTH due to hyperphosphatemia. The target range for intact PTH is < 70 pg/mL for Stage 3 CKD and < 110 pg/mL for Stage 4 CKD. Those with stage 5 have a higher target range of <300 pg/mL (K/DOQI, 2003). The mean values listed above for study MB101029 fall at or somewhat above the target range for moderate renal insufficiency.

3. Bone Turnover Markers

In the clinical development program, urinary and serum biomarkers were evaluated in Phase 3 studies over 24 weeks of short-term treatment and up to an additional 78 of long-term treatment. The sponsor reports that the mean change from baseline in the markers of bone resorption was found to be slightly higher in dapagliflozin-treated subjects compared with placebo-treated subjects. However, change in bone formation markers was inconsistent. Therefore, the sponsor states that a definitive conclusion on the net effect of treatment of humans with dapagliflozin on bone turnover (resorption/formation) cannot be made at this time.

Brief Summary of clinical studies containing biomarkers:

- MB102013: A RD/PC, Phase 3 study comparing the change in HbA1c after 24 weeks and 102 weeks, in patients taking dapagliflozin [2.5mg, 5mg and 10 mg] either in the AM (group 1) or PM (group 2).
- MB102014: A RD/PC, Phase 3 study comparing the change in HbA1c after 24 weeks and 102 weeks, in patients taking dapagliflozin [2.5mg, 5mg and 10 mg] + open-label metformin.
- MB102030: A RD/PC, Phase 3 study comparing the change in HbA1c after 24 weeks and 48 weeks, in patients taking dapagliflozin [5 mg, 10 mg] + pioglitazone. Group 1- stable pioglitazone treatment (30-45 mg/day and HbA1c 7-10.5%) or Group 2 (DM drug naïve, stable pio (15 mg/d or rosiglitazone, any dose), monotherapy with metformin or sulfonylurea. No bone biomarkers were obtained after week 24.
- MB10232: A RD/PC, Phase 3 study compare the change in HbA1c after 24 weeks in patients taking dapagliflozin [1 mg, 2.5 mg, or 5 mg] administered once daily
- D1690C00012: A RD/PC, Phase 3 study compare total body weight after 24 weeks and 102 weeks in patients with T2DM and inadequate glycemic control (HbA1c $\geq 6.5\%$ and $\leq 8.5\%$)T2DM following dapagliflozin 10 mg + metformin. DXA vs placebo +metformin. The BMD by DXA was obtained at the lumbar spine (L1-L4), femoral neck and total hip. DXA was also used to assess lean tissue mass and percent total and body fat mass (secondary endpoints).Males (age30-75) and females (55-75) were enrolled. Female subjects had to be postmenopausal (or hysterectomy). Subjects with a T-score < -2 , vitamin deficiency, bone metabolism disorders or osteoporotic fractures were excluded.

The mean change and range for each biomarker are listed in **Table 16**.

Table 16: Bone Turnover Markers

	Study /biomarker	Mean baseline value (Min, max) Long-term exposure population		Short Term Mean Range Across dose groups Mean min, Mean max	Mean Placebo Group	Long-term Mean (mean change from baseline) Across dose groups	Placebo Mean (mean change from baseline)	DAPA Trend		
Dapagliflozin 2.5 mg Vs placebo	MB102013*	CTX	All subjects*	0 333 (0 030, 1 54) N=537	0 392, 0 435 (0 044, 0 090)	0 3614 (0 002)	0 2403 – 0 3137 (-0 72, -0 019)	0 2687 (-0 085)	equivocal sCTX ↑ in ST but small ↓ in LT	
			Pre-MP*	0 310 (0 030, 0 962) N=249						
			Post-MP *	0 385 (0 077, 1 54) N=162						
		NTX	All subjects*	8 536 (3 4, 29 2) N=541	8 88, 10 10 (0 79, 1 41)	9 46 (0 44)	9 33 – 10 53 (0 79, 1 76)	10 77 (1 82)	↑ sNTX Not dose-related	
			Pre-MP*	7 6 (3 4, 19 4) N=113						
			Post-MP *	9 325 (4 2, 29 2) N=161						
		OC	All subjects*	16 035 (5 3, 57 3) N=538	16 28, 18 86 (0 81, 3 03)	18 32 (0 39)	14 39, 18 51 (-1 10, 1 23)	15 90 (-1 79)	Equivocal OC ↑ in ST, ↔ in LT	
			Pre-MP*	13 442 (5 3, 30 7) N=111						
			Post-MP *	18 470 (6, 57 3) N=160						
	P1NP	All subjects*	40 307 (10, 117 7) N=536	38 72, 41 71 (-1 37, 4 43)	41 52 (-1 31)	25 65, 36 50 (-11 78, -3 81)	30 18 (-11 18)	↓ P1NP Not dose-related		
		Pre-MP*	36 865 (11 6, 106 6) N=109							
		Post-MP *	43 988 (10, 117 7) N=161							
	Dapagliflozin 2.5mg Vs placebo + open label metformin	MB102014	CTX	All subjects*	0 27 (0 03, 1 0) N=519	0 30-0 31 (0 04, 0 06)	0 26 (-0 01)	0 26, 0 30 (-0 01, 0 01)	0 25 (-0 03)	No change sCTX
				Pre-MP*	0 23 (0 05, 1 0) N=92					
				Post-MP *	0 33 (0 06, 0 96) N=150					
NTX			All subjects*	8 14 (5 3, 25 1) N=518	8 80-9 48 (0 70, 0 90)	8 05 (0 18)	10 29, 10 76 (1 87, 2 42)	9 82 (1 58)	↑ sNTX	
			Pre-MP*	7 34 (5 3, 19 2) N=93						
			Post-MP *	9 2 (5 3, 25 1) N=150						
OC			All subjects*	13 8 (3 2, 38 9) N=520	13 09, 15 10 (-0 31, -0 20)	13 07 (-0 89)	13 78, 14 56 (-0 95, 0 46)	13 67 (-0 14)	slight ↑ OC	
			Pre-MP*	12 4 (4 3, 30 7) N=93						
			Post-MP *	16 2 (4, 38 9) N=150						
P1NP		All subjects*	34 80 (6 3, 125 5) N=520	30 27, 36 91 (-1 73, -2 76)	31 37 (-3 29)	27 74, 29 63 (-9 61, 5 46)	26 29 (-10 31)	↓ P1NP		
		Pre-MP*	32 70 (10 2, 125 5) N=92							
		Post-MP *	41 54 (13, 120 6) N=150							
Dapagliflozin 5 mg Vs placebo + pioglitazone		MB102030	Serum CTX	All subjects	PLA+PIO 0 32 DAP+PIO 0 32, 0 35	0 37, 0 45 (0 05, 0 09)	0 31 (-0 013)		↑ sCTX dose effect [†]	
			Serum NTX	All subjects	PLA+PIO 9 41 DAP+PIO 9 35, 9 68	11 33, 12 31 (2 05, 2 27)	9 85 (0 319)		↑ sNTX dose effect	

	Study /biomarker	Mean baseline value (Min, max) Long-term exposure population		Short Term Mean Range Across dose groups Mean min, Mean max	Mean Placebo Group	Long-term Mean (mean change from baseline) Across dose groups	Placebo Mean (mean change from baseline)	DAPA Trend
+ pioglitazone	OC	All subjects	PLA+PIO 15 22 DAP+PIO 15 14, 16 28	17 09, 19 32 (1 08, 2 88)	16 57 (1 068)			↑ OC dose effect
	P1NP	All subjects	PLA+PIO 33 97 DAP+PIO 32 49, 35 54	34 49, 41 14 (1 61, 5 24)	34 43 (-0 107)			↑ P1NP dose effect
Dapagliflozin 1 mg 2.5 mg 5 mg Vs placebo	MB10232			24 weeks		N/A		
	Serum CTX	All subjects	PLA 0 29 DAPA 1-5mg 0 30, 0 31	0 35, 0 43 (0 05, 0 07)	0 33 (0 04)			↑ CTX No dose effect
	Serum NTX	All subjects	PLA 8 56 DAPA (1-5mg) 8 68, 10 11	9 95, 11 73 (1 30, 1 97)	10 61 (2 01)			↑ NTX No dose effect
	OC	All subjects	PLA 15 77 DAPA (1-5mg) 15 54, 18 32	17 15, 20 38 (0 58, 1 80)	17 21 (1 36)			↑ OC No dose effect
	P1NP	All subjects	PLA 35 31 DAPA (1-5mg) 33 35, 38 36	35 56-41 22 (-1 45, 2 37)	34 88 (-0 51)			↑ P1NP
Dapagliflozin 10 + metformin Vs placebo + metformin	D1690C00012			24 weeks		50 weeks		
	Serum CTX	All subjects	0 22 Dapag 0 24 PLA	NR (0 03)	NR -0 01	0 26 (0 04)	0 26 (0 02)	no change compared to PBO sCTX
		PMP pop	Not available					
	Serum NTX	All subjects	8 91 PLA 9 00 DAPAG	NR (0 27)	NR (-0 15)	8 64 (-0 36)	8 34 (-0 57)	decrease but effect not greater than PBOsNTX
		PMP pop	Not available					
	OC	All subjects	14 07 DAPA 15 20 PLA	NR (-0 46)	NR (-1 50)	13 67 (-0 40)	13 21 (-1 99)	↓ OC
		PMP pop	Not available					
	P1NP	All subjects	26 72 DAPA 28 19 Pla	NR (-0 04)	NR (-1 96)	25 93 (-0 79)	24 45 (-3 74)	↓ P1NP
		PMP pop	Not available					
	Urine CTX	All subjects	8 76 DAPAG 10 49 PLA	NR (0 69)	NR (-0 06)	9 86 (1 10)	10 21 (-0 27)	↑ uCTX
		PMP pop	Not available					
	Urine NTX	All subjects	275 2 DAPAG 314 4 PLA	NR (-24 32)	NR (-11 10)	243 4 (-31 8)	271 4 (-43 0)	↓ uNTX
		PMP pop	Not available					
	BSAP	All subjects	17 06 DAPA 17 03 PLA	NR (-0 97)	NR (-1 33)	16 26 (-0 80)	15 42 (-1 61)	↓ BSAP
PMP pop		Not available						

*data from long term study datasets
Values for study MB102013 represent Group 1 only (Hb 7-10)
ST=short term, LT=long term, NR=not reported
Pre-MP=premenopausal, post-MP=postmenopausal

Reviewer's comments: 1) In the two long-term studies with available datasets (≥ 50 weeks duration), the mean baseline range in bone turnover markers for postmenopausal subjects appeared only slightly higher than those for the premenopausal subjects. Therefore, these data may not be applicable to postmenopausal women in whom one would expect to see increased bone turnover. Normal ranges for postmenopausal and premenopausal women are not widely published due to the high biologic variability between populations. Furthermore, the approved use of these markers is for the management of individual patients with osteoporosis.

2) Overall, there were small inconsistent changes in bone turnover markers, including bone resorption. No conclusions can be made from these data. This is in agreement with the sponsor's overall assessment.

4. Bone Mineral Density

The effect of dapagliflozin on bone mineral density is being specifically evaluated in study D1690C00012 with bone assessments performed at the end of Years 1 and 2. The effects of dapagliflozin on bone mineral density is measured by DXA, along with the evaluation of biochemical markers of bone formation and bone resorption. Twenty-four week safety data from the short-term period of D1690C00012 are included in the SCS; 1-year DXA data from this study was not initially included because the data just became available the first half of 2011 (however, an updated DXA dataset (ADDU) was submitted on May 27, 2011 and is included in this review). The sponsor believes that based on available results from Phase 1, 2, and 3 studies in humans as well as studies in laboratory animals, there are no clearly identified risk for adverse effects on bone health in subjects treated with dapagliflozin at doses of 2.5 to 10 mg per day.

Review of 4-Month safety update for Study D1690C00012:

Of the 182 randomized, 165 remained after the 50 week visit (84 on placebo and 81 on dapagliflozin). Nine subjects were discontinued due to pre-specified change in T-score BMD (T-score <-2.5 or T-score change $>5\%$ - 3 on placebo, 6 on dapagliflozin). All discontinuations were due to 5 to 10% decrease at one site. The mean duration of T2DM was 5.77 years with 16.7% having T2DM for over 10 years. Mean HbA1c was 7.2%. A 2% difference at Week 50 was deemed clinically relevant. See **Table 17**.

Table 17: Mean Percent Change in BMD at the LS, FN, and TH at 50 Weeks (95% CI) Sponsor's data

	Dapagliflozin	Placebo	Difference in adjusted percent change (95% CI) compared to placebo
Lumbar spine (LS)	0.25 (-0.41, 0.92)	0.15 (-0.50, 0.81)	0.10 (-0.83, 1.04)
Femoral Neck (FN)	-0.47 (-1.13, 0.19)	0.15 (-0.51, 0.81)	-0.62 (-1.54, 0.32)
Total Hip (TH)	-0.02 (-0.73, 0.70)	-0.23 (-0.94, 0.48)	0.22 (-0.79, 1.24)

Source: 4-Month Safety update, Appendix 5, p.190

Reviewer's comment: Study discontinuation was based on BMD change: Per the study protocol, subjects would be discontinued if the T-score fell below ≤ -2.5 or if there was a $\geq 5\%$ decrease in T score at the lumbar spine, femoral neck or total hip compared to baseline. T-score is used to classify or diagnosis osteoporotic or osteopenia and is not generally used to measure bone loss over time in clinical trials. Actual change in BMD is the appropriate measure of bone loss. Usually a change of $>7\%$ in BMD from baseline at lumbar spine or total hip at any post-baseline time is a criterion for discontinuation. A cut-off of 5% was used by this reviewer in order to capture all events reported by the sponsor.

In an Information Request dated 5/26/11, this reviewer requested the six narratives of subjects who were discontinued due to T-score BMD loss at one site. The sponsor subsequently submitted six narratives. The 4-month safety update actually reports nine subjects fulfilling this criterion. Note: The actual T-score change was not indicated in the narrative. The narratives only stated "decrease in BMD at DXA

measurement, T-score ≤ -2.5 or $\geq 5\%$ decrease in T-score for BMD at LS, FN or TH compared to baseline.”

A follow-up Information Request was sent on May 31, 2011, for clarification and included a request for the remaining narratives. Available narratives for outliers based on actual percent change in BMD $>5\%$ are summarized below. The narratives contain limited clinical data but were merged with data from the dexa dataset (BMD change data). No subject had $> 5\%$ change in BMD at more than one site.

Narratives: Discontinuations based on $>5\%$ BMD change from baseline

Dapa+ Metformin

- D1690C00012-104-5: A 59 yo white male with DM, obesity, HTN, chronic pyelonephritis and decreased bone density (BMD change of -7.6% from baseline at the FN) noted on study Day 358. Meds: amlodipine, HCTZ. Study drug was discontinued.
- D1690C00012-202-2: A 59 yo white male with DM, HTN, CAD, dyslipidemia, former smoker with decreased bone density (BMD change of -7.6% at the LS) noted on Day 366. Study drug was discontinued. Meds: ASA, atorvastatin, metoprolol, perindopril, calcium, vit D.
- D1690C00012-304-27: 56 yo white female with DM, HTN, dyslipidemia, obesity, and decreased bone density density (BMD change of -6.5% at the LS) noted on Day 350. Study drug was discontinued. Meds: ASA, atorvastatin, HCTZ/Losaratan.
- D1690C00012-502-10: 73 yo white male with DM, HTN, URI with decreased bone density (BMD change of -8.5% at the LS) noted on Day 350. Study drug was discontinued. Meds: glucosamine, amlodipine, enalapril.

Placebo+Metformin

- D1690C00012-301-1: 54 yo white male with DM, HTN, dyslipidemia, knee arthralgia, smoking history with decreased bone density (BMD change of -5.3% at the TH) on Day356. Study drug was discontinued. Meds: ASA, clopamide, perinopril, potassium, simvastatin.
- D1690C00012-304-3:65 yo white female with DN, HTN, dyslipidemia, arthralgia, Lyme’s disease with decreased bone density (BMD change of -9.4% at the LS) on Day 354. Study drug was discontinued. Meds: amlodipine/atorvastatin, bisoprolol, chondroitin, cholecalciferol, nimesulide, doxycycline

In response to an Information Request, the sponsor submitted an updated ADDU dataset (via email on May, 27, 2011) containing 50-week DXA data from 166 subjects (82 dapagliflozin/metformin and 84 in the placebo/metformin group). The results differ slightly from the sponsor’s reported results. This cannot be solely explained by the difference in patient numbers (165 vs 166). See **Table 18**.

Table 18: 50 Week Data – Percent change from baseline (min change, max change)

	Dapa 10mg + Met (n=82)	Placebo + Met (n=84)
LS BMD	0.26 (-8.5, 8.9)	0.18 (-9.4, 8.1)
Femoral Neck	-0.42 (-8, 4.6)	0.17 (-6.4, 12.7)
Total Hip	0.1 (-7.2, 36.1)	-0.23 (-5.3, 4.6)

Table 19 shows the BMD outliers defined as change from baseline > 5 %:

Table 19: BMD Lumbar spine (50 week results)

USUBJID	AGE	SEX 1/male 2/female	DUDY	WEEK	RESULT	Baseline Value	% Change from baseline
Dapagliflozin Group							
D1690C00012-202-2	59	1	366	50	1.002	1.084	-7.6
D1690C00012-209-14	59	1	351	50	1.253	1.174	6.7
D1690C00012-304-27	56	2	350	50	1.142	1.221	-6.5
D1690C00012-310-3	59	2	334	50	0.887	0.838	5.8
D1690C00012-502-10	73	1	362	50	1.104	1.207	-8.5
D1690C00012-502-17	65	1	351	50	1.24	1.139	8.9
Placebo Group							
D1690C00012-209-10	56	2	357	50	1.022	1.091	-6.3
D1690C00012-304-3	65	2	354	50	0.878	0.969	-9.4
D1690C00012-304-30	52	1	353	50	1.355	1.253	8.1
D1690C00012-404-2	43	1	350	50	1.184	1.104	7.2
D1690C00012-501-3	66	1	348	50	1.101	1.036	6.3
D1690C00012-502-3	59	2	352	50	1.249	1.186	5.3
D1690C00012-502-8	66	1	349	50	1.504	1.431	5.1

Source: ADDU dataset submitted 5-31-11

BMD Femoral Neck results

USUBJID	AGE	SEX 1/male 2/female	DUDY	WEEK	RESULT	Baseline Value	% Change from baseline
Dapagliflozin							
D1690C00012-104-5	59	1	358	50	0.868	0.939	-7.6
D1690C00012-203-1	59	2	359	50	0.75	0.795	-5.7
D1690C00012-304-29	51	1	354	50	1.031	1.121	-8
Placebo							
D1690C00012-101-6	60	2	358	50	0.801	0.711	12.7
D1690C00012-208-2	69	2	379	50	0.843	0.759	11.1
D1690C00012-210-4	59	2	354	50	0.908	0.846	7.3
D1690C00012-303-8	60	1	350	50	0.891	0.847	5.2
D1690C00012-306-8	68	2	355	50	0.956	0.905	5.6
D1690C00012-404-3	56	1	377	50	0.999	1.067	-6.4
D1690C00012-501-3	66	1	348	50	0.878	0.831	5.7

BMD Total Hip results

USUBJID	AGE	SEX 1/male 2/female	DUDY	WEEK	RESULT	Baseline Value	% Change from baseline
Dapagliflozin							
D1690C00012-108-8	73	2	358	50	0.714	0.769	-7.2
D1690C00012-202-3	54	1	350	50	1.475	1.084	36.1
D1690C00012-501-4	64	2	345	50	0.965	0.911	5.9
Placebo							
D1690C00012-301-1	54	1	356	50	0.902	0.952	-5.3

Reviewer's comment: Mean data suggest minimal effects of dapagliflozin on BMD at 50 weeks. Outliers show that there were 7 subjects in the dapa group and 3 subjects in the placebo group with losses of approximately 9%. Conversely, many subjects had BMD increases (5 dapagliflozin, and 11 placebo). A difficult to explain 36% increase in BMD was seen in one subject, but generally increases ranged up to about 12%.

Off-target SGLT1 effects: Due to the cross-reactivity of dapagliflozin at the SGLT site, potential effects at SGLT-1 were investigated to determine if the noted alterations could be attributed to off-target effects and not related to bone metabolism.

SGLT-1 is also found in the small intestine and myocytes. Based on IC50s, dapagliflozin is expected to be highly potent at SGLT2 and 1600 fold less potent at SGLT1. Potencies (IC50s) for Dapa SGLT1 are 1600 nM, SGLT2: 1.0 nM. As a reference, potencies for canagliflozin are SGLT1: 664 nM, SGLT2: 4 nM.

Cardiac Effects:

SGLT-1 is found in the myocyte 10-fold higher than in kidney and may have a functional role in cardiac glucose transport, particularly, a positive inotropic effect. Since dapagliflozin is an inhibitor of SGLT-1, cardiovascular events of interest would most likely be related to negative inotrope activity, i.e., heart failure.

Cardiovascular metaanalysis: An independent blinded adjudication process was generated for cardiovascular events. This metaanalysis was based on evidence from recent trials that some therapies may increase the risk of cardiovascular events and in accordance with the December 2008, FDA Guidance for Industry, "Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." The primary objective was the relative risk ratio on the primary composite endpoint of adjudicated CV death, MI, stroke, and hospitalization for unstable anginas. The secondary endpoint was a composite of all those from the primary endpoint plus unplanned coronary revascularization and hospitalization for heart failure.

Baseline characteristics of the 14 Phase 2 and 3 studies contributing to the meta-analysis included the study population had a mean age of around 56 years and approximately 20% were ≥ 65 years of age. Mean body mass index (BMI) was 31.5 kg/m². The mean duration of T2DM was 6 years, and approximately 20% had a duration of diabetes over 10 years. Approximately 50% of the subjects had dyslipidemia, approximately 2% had congestive heart failure (CHF) and more than 60% had hypertension at baseline. Almost 20% of the subjects had a history of CV disease other than hypertension. eGFR values showed that half of the subjects had Stage 2 (mild) chronic kidney disease (CKD) (≥ 60 and < 90 mL/min) and around 11% had Stage 3 (moderate) CKD (≥ 30 and < 60 mL).

Results: The results did not show an increase in for the primary endpoint 0.674 (98% CI: 0.385, 1.178; 95% CI: 0.421, 1.078) during the ST + LT period or secondary endpoint 0.632 (98% CI: 0.385, 1.036; 95% CI: 0.416, 0.959) during the ST + LT period. Both

measures met the pre-specified upper limit goal of < 1.8 for the 2-sided 95% CI for the estimated risk ratio.

Based on inhibition of SGLT-1, heart failure is a target of interest. The secondary composite endpoint included heart failure. Based on 4-Month Safety Update, the dapagliflozin group reported there were 5 events (out of 60 events) of hospitalization for heart failure compared to 7 (out of 42 events) in the comparator group. See **Table 20**.

Table 20: Cardiovascular metaanalysis: Secondary composite endpoint

	Dapa N=60 subjects with first events	Comparator (placebo/metformin/glipizide) N=42 subjects with first events
Hospitalization for Heart failure	5	7
CV death	7	4
MI	13	14
Stroke	11	5
Hospitalization for unstable angina	11	4
Unplanned coronary revascularization	13	8
Source: CV metaanalysis report, 4-Month Safety Update (4/28/11)		

Reviewer’s comment: Overall, in the cardiovascular metaanalysis, there were more cardiovascular first-events in the dapagliflozin group (60 vs 42) in the secondary analysis, but there was not an increase in the number of subjects with hospitalization for heart failure compared to the comparator group (5 vs 7). Therefore, no CV signal can be attributable due to SGLT-1 inhibition at the heart.

Gastrointestinal effects:

SGLT1 is also found in the gastrointestinal tract. SGLT1 is expressed on the brush border of most mammalian species with higher levels in the jejunum>duodenum> ileum but not in the large intestine. SGLT1 is the major route for transport of dietary sugars from the lumen to the intestine into enterocytes (Shirazi-Beechey et al., 2011). Inhibition of SGLT1 would inhibit glucose and galactose absorption leading to some form of malabsorption leading to diarrhea, dehydration, and weight loss. A genetic form of is rarely seen in infants due to lack of the SLC5A1 gene. See **Table 21**.

Table 21: Gastrointestinal and Dehydration Events

	Dapa N=4287	Comparator (placebo/metformin/glipizide) N=1941
Gastrointestinal disorders, all	885 (20.6)	402 (20.7)
Diarrhea	220 (5.1)	123 (6.3)
Dehydration	8 (0.2)	2 (0.1)
Source:ISS, Appendix 89A Original NDA submission		

Reviewer’s comment: No significant differences were seen in GI disorders or events of dehydration.

Vascular tissue mineralization/hyperostosis:

In an attempt to determine if off target mineralization or hyperostosis was increased we examined the rate of musculoskeletal and connective tissue disorders. For the short and long term studies, the rates between dapagliflozin and comparators were similar.

Table 22: Musculoskeletal Effects – Short + Long-term (Source: Appendix 89A)

	Dapa N=4287	Comparator (placebo/metformin/glipizide) N=1941
Musculoskeletal and CT disorders	761 (17.8)	337 (17.4)
Source:ISS, Original NDA submission		

Conclusions:

- No clinically significant changes were seen in laboratory values including calcium, 25-OH vitamin D, Magnesium, Phosphorus or PTH. Elevated baseline PTH levels are common in renal insufficiency which can also promote hyperphosphatemia.
- Mean data show minimal effects of dapagliflozin on BMD at 50 weeks. Outliers show increased bone loss, in addition to bone formation (consistent with animal studies.)
- The bone biomarkers are uninterpretable. Overall, there were small inconsistent changes in both bone resorption and bone formation.
- Fracture occurrence was infrequent in the clinical program (<1%). Despite an imbalance seen in subjects with moderate renal dysfunction in study MB102029, there was not an imbalance in the pooled moderate renal dysfunction population. The imbalance may be attributable to an older population who could have had undiagnosed osteoporosis at baseline along with concomitant fall risks (e.g. neuropathy, peripheral vascular disease/amputation, osteoarthritis, and fasting state). It is well-recognized that the propensity to fall is a risk factor for fracture and is independent of bone mineral density. The increase in fractures in patients with normal renal function is difficult to explain based on the available data; however, these fractures generally occurred in subjects who were at risk for osteoporosis based on age. In addition, the increased rates of hypotension and/or neuropathy suggest that these fractures may be unrelated to bone physiology and more likely related to acute and chronic risk factors for falls. Baseline osteoporosis (based on T score < -2.0) was an exclusion criterion for only one study (D1690C00012), thereby increasing the chance of pre-existing bone disease in the overall patient pool. Furthermore, subjects in MB102029 had longer mean durations of DM (16.9 years) putting them at greater risk for diabetic complications such as neuropathy.

- Negligible changes in laboratory values were also noted. Overall, the apparent imbalances do not appear to be significant.

In summary, from the data reviewed, there is no indication that dapagliflozin exerts a clinically significant effect on bone loss or fracture. Full review of the 2-year data would be reassuring but generally would not be required for approval from a bone standpoint. While bone loss due to weight loss is a primary concern, further surveillance of bone formation/hyperostosis based on nonclinical evidence of vascular tissue mineralization, and increased bone resorption should also be monitored. We note that Study D1690C00012 is ongoing and data from 102 weeks of exposure will be provided when available.

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/s/

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07/18/2011

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 29, 2011

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II, OND, CDER

Through: Solomon Iyasu, MD, MPH, Director
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER
Diane K Wysowski, PhD, MPH, Team Leader
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From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology, OSE, CDER

Subject: (b) (4)


Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-1273

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JING JU
07/11/2011

SOLOMON IYASU
07/12/2011



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 29, 2011

To: Mary Parks, MD, Director
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From: Julia Ju, PharmD, PhD, Pharmacoepidemiologist
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Subject: (b) (4)


Drug Name(s): Dapagliflozin

Submission Number:

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JING JU
07/08/2011

SOLOMON IYASU
07/08/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Division of Pharmacovigilance 1**

Date: 21 June 2011

To: Mary Parks, MD, Director
Division of Metabolic and Endocrine Products

Reviewer: Leonard Seeff, MD, Hepatologist
John Senior, MD, Hepatologist
Office of Surveillance and Epidemiology

Through: Allen Brinker, MD, MS, Medical Team Leader
Division of Pharmacovigilance 1

Mark Avigan, MD, CM, Associate Director,
Office of Surveillance and Epidemiology

Drug Name: Dapagliflozin

NDA Number: 202293

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1474

Issue: Review of cases of serious liver toxicity arising in
NDA 202293 (dapagliflozin)

INTRODUCTION

Based on the consult request, dapagliflozin is an inhibitor of SGLT2 (sodium glucose cotransporter 2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin results in the direct, and insulin-independent, elimination of glucose by the kidney. The Agency is currently evaluating dapagliflozin (as NDA 202293) which, if approved, will be a first-in-class treatment of Type 2 Diabetes.

The primary assessment of safety in subjects with T2DM has been based on three Phase 2b and eleven Phase 3, double-blind, placebo/active-controlled, randomized clinical studies. Dapagliflozin was administered as:

- Monotherapy in 4 studies.
- Add-on combination therapy with other antidiabetic medication in 6 studies.
- Initial combination therapy with metformin in 2 studies.
- A direct comparison with SU.
- Monotherapy in subjects with moderate renal impairment.

In total, over 4000 subjects with T2DM have been exposed to dapagliflozin (2.5 mg or higher) and 2000 subjects were exposed to the 10 mg dose in the Phase 2b and 3 clinical program. Overall, there were 2.2 times as many subjects exposed to dapagliflozin (N = 4,287), compared with control (N = 1,941).

For patients treated or randomized to dapagliflozin (N=4,287), patient counts by exposure window are as follows:

- 3,333 @ 6 months
- 2,232 @ 12 months
- 1,317 @ 18 months
- 441 @ 24 months

Cumulative exposure to dapagliflozin in Phase 2b and 3 studies was 4009.1 patient-years and 1681.9 patient-years to control. Based on these metrics, the average duration of observation in dapagliflozin arms was 341 days and 316 days in control arms.

During review, it has come to the attention of DMEP that there have been at least 8 cases treated with dapagliflozin who developed liver-related test dysfunction with elevations of both serum ALT and bilirubin in the clinical development program for dapagliflozin. Among the 8 cases, 5 reported values that reached the laboratory threshold¹ for potential Hy's Law cases. Of note, nonclinical findings with dapagliflozin were minimal. There was some hepatic toxicity in the one month rat and dog studies, but at very high multiples of the human exposure dose. Also, the 6 month rat study and 12 month dog studies had increased liver weights.

¹ ALT or AST > 3X ULN and concomitant or subsequent TBL > 2X ULN within 30 days after discontinuation of study medication

Given the regulatory importance of a validated case(s) of liver injury consistent with Hy's law based on the FDA Guidance Document² and based on currently available data³, DMEP requested review of case summaries for the 8 patients with elevated serum ALT and bilirubin levels including 5 that are consistent with Hy's Law for validation as Drug-Induced Liver Injury (DILI). In addition, DMEP requested review of 27 other cases in dapagliflozin-treated individuals and two patients on blinded treatment identified by the sponsor with a clinical or laboratory assessment of liver injury not included in the 8 cases with reported elevations of both serum ALT and bilirubin.

BACKGROUND

The Guidance document is quite clear on the regulatory impact of Hy's Law cases for drugs in their clinical development program. This is outlined in the following text extracted from the Guidance:

'Hy's Law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. '...

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population. Clinical trials of the beta blocker dilevalol

² Guidance for Industry – Drug-Induced Liver Injury: Premarketing Evaluation. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

³ Including case narratives from the Four Month Safety Update (4MSU), SCS Appendices, and Report of the Independent Adjudication Committee for Adverse Hepatic Events

(enantiomer of labetalol, a diastereoisomeric mixture) showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. This led to a request for a much larger premarketing database and the drug was abandoned.

Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of the so-called Hy's Law cases.⁴ This observation was recently confirmed in large studies of DILI in Spain⁵ and in Sweden⁶ in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants. Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing.⁷

Thus, due diligence on the part of drug sponsors and the Agency is necessary in pursuit Hy's Law cases in drug development programs.

METHODS AND MATERIALS

Case narratives and other information were reviewed from materials provided to OSE from DMEP. These materials were limited to:

- Four Month Safety Update (4MSU)
- SCS Appendices
- Report of the Independent Adjudication Committee for Adverse Hepatic Events with cases and data elements reported through 15-Oct-2010.

A grading system of probabilistic causal association developed by the NIH Drug-Induced Liver Injury Network (DILIN) Study has been used in this analysis.⁷ This grading system has been applied by DILIN in the analysis of causality of cases of liver injury that have occurred in patients in a clinical practice setting treated with marketed drugs who were then referred to the DILIN network for evaluation. The grading of causal association with a particular drug is as follows: Definite - >95% likelihood; Highly Likely = 75% to 94% likelihood; Probable = 50% to 74%; Possible = 25% to 49%, Unlikely = <25%.

⁴ Temple, R, 2001, Hepatotoxicity Through the Years: Impact on the FDA, presented 2/12/2001, <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm122149.pdf>.

⁵ Andrade, RJ, MI Lucena, and MC Fernandez et al., 2005, Drug-Induced Liver Injury: An Analysis of 461 Incidences Submitted to the Spanish Registry Over a 10-Year Period, *Gastroenterology*, 129(2):512-21.

⁶ Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, *Hepatology*, 42(2):481-9.

⁷ Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009; 32 (1):55-68.

SUMMARY OF RESULTS AND DISCUSSION

Eight cases with elevated serum ALT and bilirubin were identified and among these 5 reported laboratory values consistent with potential Hy's law (serum ALT > 3X ULN and bilirubin > 2X ULN), conditional upon finding that the liver problems were not principally cholestatic and that no alternative probable cause could be found after reasonable and thorough search, as identified by the sponsor are outlined in Table 1. These cases were identified through inspection of a table which begins on page 11 of the Hepatic Adjudication Report as prepared by the sponsor. All individuals received dapagliflozin. A summary of each of these cases follows on the following page as Table 1.

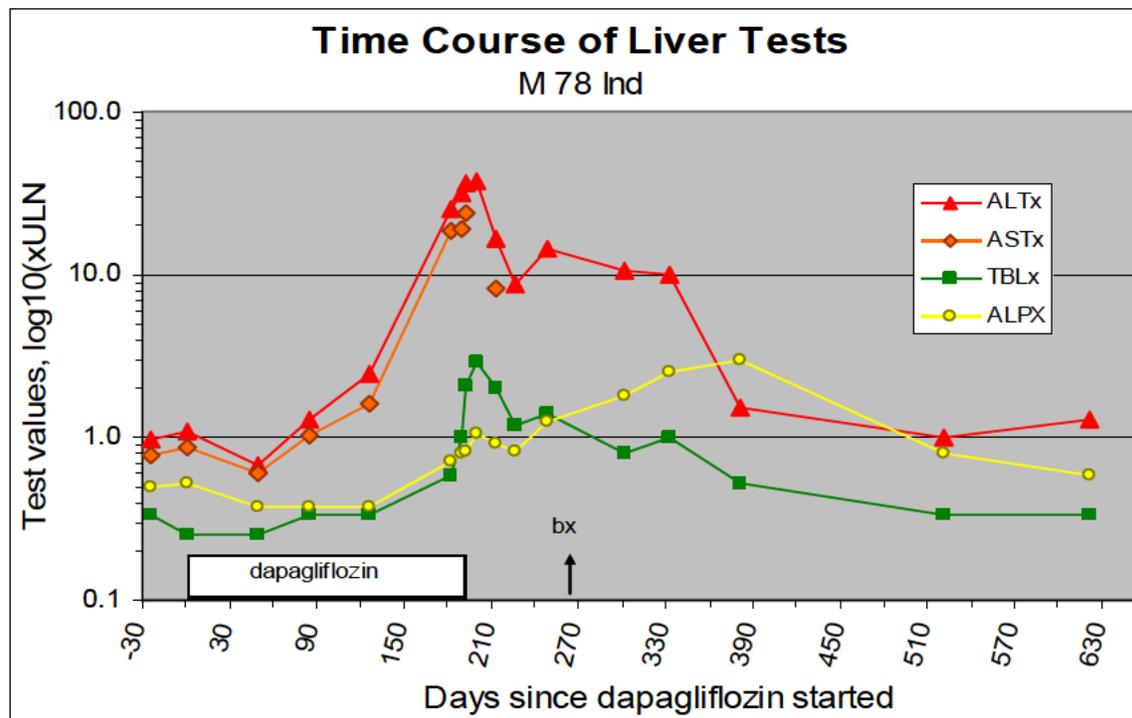
Table 1. Reformulation of Table 3.1 from sponsor's Hepatic Adjudication Review listing 8 dapagliflozin-treated cases with elevated serum ALT and bilirubin levels, including 5 consistent with Hy's Law and FDA assessment of drug causality.		
	ID	Causality per CDER
1	D1690C00004-4402-6	Probable
2	D1690C00005-6008-10	Unlikely
3	D1690C00005-6013-3	Unlikely
4	D1690C00005-7002-4	Unlikely
5	D1690C00006-1511-6	Unlikely
6	D1690C00006-2004-6	Not DILI
7	D1690C00012-403-1	Insufficient data
8	MB102030-9-92	Unlikely

Case narratives for the 8 cases with elevations of serum ALT and bilirubin identified by the sponsor.

D1690C00004-4402-6: 78 year old man from India with type 2 diabetes, coronary artery disease, hypertension, dyslipidemia and benign prostatic hypertrophy, Participated in the trial and received the study drug plus metformin. Concomitant drugs included atorvastatin, cromolyn, lecanlidipine, atenolol, parendopril, naproxen, acetylsalicylic acid and a couple of herbal products. The patient also carried a diagnosis of hemochromatosis, C282Y/H63D compound heterozygote.

At baseline, the ALT value was slightly increased and the AST was normal. On day 85 of treatment, he was found to have an ALT value of 62 (no AST performed) that reached a value of 1204 on day 183 with an AST of 825, an alkaline phosphatase (ALP) level of 103 and a serum total bilirubin of 0.7. His prothrombin time was 12.4 seconds and his INR was 1.2. The study medication was discontinued on day 191. The values peaked on day 200, as follows: ALT, 1858, AST (day193) 1060, ALP 128, bilirubin 4.2. The serum

biochemical time course associated with the liver injury event in this study subject is outlined in the figure on the following page.



A liver biopsy was performed (b) (6) read by two different pathologists. The report indicated that, “there is evidence of hepatitis with severe inflammatory activity of relatively short duration. However, the presence of prominent interface hepatitis and associated pattern of fibrosis in periportal regions favors progression to chronic hepatitis. Underlying etiology is uncertain. Viral agents, drugs, and autoimmune hepatitis are three main possibilities to be considered in the differential diagnosis and a number of histologic features would favor a diagnosis of autoimmune hepatitis. However, results of other investigations do not appear to support this diagnosis. The clinical presentation appears to favor drug toxicity as a likely cause of liver injury. Siderosis is mild and has a mixed parenchymal / mesenchymal distribution. This finding suggests that there is unlikely to be significant liver injury related to genetic iron overload.” On day 349, it was decided to treat with prednisolone for 4 weeks. Thereafter, all values began a slow decline reaching near normal values approximately 6 months later and remained normal thereafter.

Workup for other etiologies revealed that serologic markers for hepatitis A, B and E were negative. The test for hepatitis C at baseline was negative but it was not repeated later. Serologic markers for autoimmune hepatitis were all negative even though the liver biopsy had some suggestive features of AIH with acute necro-inflammation and interface hepatitis. CMV IgG and EBV IgG were both positive implying past infection and the

patient had increased transferrin levels. During treatment, the patient developed back pain associated with findings of osteoporosis.

Comment: Based on these data, despite the histology with features suggestive of autoimmune hepatitis, and even though treatment with corticosteroids was initiated after which liver chemistries improved, a definitive diagnosis of autoimmune hepatitis seems unlikely, since the acute injury developed for the first time in an older male and the serologic markers of autoimmune hepatitis were negative. Such histology is by no means absolutely indicative of AIH and can be found in other causes of acute liver injury, including drug-induced liver injury. It should be noted that, with discontinuation of dapagliflozin, the serum aminotransferase and bilirubin values began a slow decline but the alkaline phosphate level continued to increase slightly before falling to a normal level; nevertheless, the pattern of liver dysfunction appeared consistent with that of an acute hepatocellular injury. It is my view, therefore, that the probable diagnosis is mild to moderately severe dapagliflozin-induced liver injury.

D1690C00005-6008-10: 55 year old white female treated with study medication. She used alcohol occasionally. She apparently had increased AST and bilirubin levels and a slight increase in ALT values at baseline and, during the course of treatment, she had intermittent increases in AST and bilirubin levels. The values peaked on day 294: AST 129, ALT 74, and bilirubin peaked on day 287. The study drug was temporarily discontinued (days 309-317) and then treatment was resumed without causing apparent further liver dysfunction. Hepatitis serology was negative. No data are supplied

Comment: The cause for the persistent but fluctuating liver-related tests that began at baseline cannot be determined from the data that are available. Regardless, given the fact that liver dysfunction already existed when use of the test drug was begun, the drug cannot be held responsible for the observed liver injury.

D1690C00005-6013-3: 83 year old white male with type 2 diabetes. Started on study drug together with glipizide. Concomitant drugs include albendazole, pantoprazole, and nutritional supplements. Patient had a history of cholelithiasis together with obstructive jaundice requiring hospitalization for papilotomy; cholecystectomy recommended but patient refused. Treatment with study drug begun 9 months later, and subsequently he develops two separate episodes of liver dysfunction. The first began on day 85 lasting presumably to day 93 (no actual levels reported). The aminotransferase values increased modestly, the ALP increasing from a baseline of about 85 to 236 associated with a slight increase in serum bilirubin. The values then returned to normal despite continued use of study drug. The second episode began on day 141- at which time the drug was discontinued- lasting presumably to day 148 when the values peaked: ALT 271, bilirubin 2.7. The values for ALP increased only slightly on this occasion. No other values given although it is stated that the values gradually returned to normal. The patient did not have symptoms during the abnormalities and the presence or absence of fever is not reported. Ultrasound showed cholelithiasis but no evidence of dilated biliary

ducts. Serology for the hepatitis viruses were reported to be negative. No markers of autoimmune hepatitis were reported but it is unlikely that the abnormalities were a result of AIH in this older man.. The patient did report taking St Johns Wort and fern before each episode of abnormality.

Comment: The patient developed 2 episodes of transient increases in liver chemistries, the first characterized by an elevation especially of the alkaline phosphatase value as well as of the serum bilirubin, and the second by mild increases in the ALT and ALP and an increase in serum bilirubin. Given the past history of gall stones for which surgery was recommended but was not done because of patient refusal, the likeliest diagnosis in this patient remains that of biliary tree disease. This is particularly so for the first episode during which ALP values increased and recovery occurred even though the drug treatment continued. The ALP during the second episode was only mildly increased which may give credence to another cause for the abnormality but, in my opinion, could still represent passage of a small stone. Thus, while DILI cannot be absolutely ruled out, the likelihood is extremely low that the study drug was responsible for the liver dysfunction.

D1690C00005-7002-4: 60 year old Asian female treated with the study drug. Develops abdominal pain, fatigue and anorexia, but without specifying the date. Ultrasound reveals small stone with sludge in distal common bile duct. The patient had multiple tests for liver chemistries during treatment and even before starting the test drug, all of which were normal. On day 278 of treatment, all liver chemistries were still normal. At the time of the next test, on day 334, the ALT was 732, the AST was 842, the ALP was 206, and the serum bilirubin 4.0. She undergoes ERCP with unsuccessful effort to remove stone, so stent is inserted with surgery planned for the future. By day 351, all liver-related biochemical values have returned to normal. There is no mention of whether the drug was stopped.

Comment: Based on what is reported, it appears that the patient develops jaundice because of extrahepatic biliary obstruction and not because of drug induced liver injury.

D1690C00006-1511-6: 61 year old white female with type 2 diabetes and diabetic complications started on study drug. Has a history of “biliary colic” with planned cholecystectomy. Preoperative liver tests all normal with the exception of an increase value for ALP (291). Ultrasound revealed cholelithiasis and fatty liver. Treatment temporarily discontinued and laparoscopic cholecystectomy performed revealing a gall bladder filled with stones. Post surgery, developed transient increases in amino-transferases and serum bilirubin. Study drug discontinued again for a few days and then re-started without further problems.

Comment: The cause of the liver dysfunction, which is only minimally described here, is almost certainly cholelithiasis and post-cholecystectomy liver dysfunction. Clearly, there is no evidence of drug-induced liver injury.

D1690C00006-2004-6: 61 year old white male begun on study drug. Concomitant medications included atorvastatin, amlodipine, irbesartan, acetylsalicylic acid, acetaminophen, chlorquinaldol, dexamethasone, hydrochlorothiazide and omeprazole. Began to lose weight on about day 97 and on day 112, developed jaundice and asthenia. Work up (not specified) revealed evidence of pancreatic cancer with hepatic metastases. Peak ALT 191, peak AST 153, peak bilirubin 31.6. ALP not reported. Study drug stopped. Patient died on day 159.

Comment: Diagnosis: Pancreatic cancer with hepatic metastases.

D1690C00012-403-1: 52 year old white male with type 2 diabetes and onychomycosis started on study drug. Concomitant drugs are itraconazole, intapamide, atenolol, ramapril, multivitamins. Also received metformin. Baseline ALT slightly elevated but bilirubin value normal. Day 29, ALT 79, AST 108, total bilirubin 1.7. On days 57, 64 and 78, ALT values 155, 187, and 150, respectively; AST values 89, 128, and 93, respectively; and total bilirubin 2.0, 1.4, and 2.2, respectively. Thereafter, values decreased slightly but remained abnormal. Investigator thought that itraconazole was responsible for the liver dysfunction. Study drug discontinued on day 91 and on day 122, the adverse event said to be resolved. No report on hepatitis serology or AIH markers. No imaging reported and no further data available.

Comment: Cannot determine cause for liver dysfunction because of paucity of data; need sequential liver tests; need evidence that the patient was evaluated for all other possible etiologies, i.e. hepatitis serologies, autoimmune markers; need to have display of all drugs received with start and stop dates for each relative to the onset of abnormal liver tests. In sum, there are insufficient data available to either rule in or rule out drug-induced liver disease and, if so, which drug.

MB102030-9-92: 60 year old white male started on study drug. Concomitant drugs include pioglitazone, allopurinol, valsartan, apap/hycod, hydromorphone, ibuprofen, acetylsalicylic acid, ondansetron, multivitamins. 164 days after starting study drug, the patient was admitted to hospital complaining of right upper quadrant pain, anorexia, nausea and vomiting. On admission, he was afebrile but had tachycardia. Physical examination revealed a soft, moderately tender right upper quadrant and epigastrium. At this time, his AST was 240, ALT 139, ALP 120 and bilirubin 2.0. Clearly, the working diagnosis was possible biliary tree disease, such as gallstones, but imaging was unrevealing although there was concern that the picture was obscured by bowel gas. Over the next 3-5 days, the aminotransferase values began to decline although the serum bilirubin increased, peaking at 7.6 on day 165. His ALP remained normal. By day 175, all values had returned to normal. Importantly, his WBC remained normal although he did develop a transient fever. Hepatitis serology tests were said to be normal. A HIDA scan was performed and was unrevealing. Also, an ERCP was planned but was not carried out. Finally, he had an MRCP scan which raised the suspicion of a gall stone at

the gallbladder neck without obvious calculi in the common bile duct. The symptoms and elevated biochemical values subsided and were apparently normal within 10 days.

Comment: The likely diagnosis in this patient with abrupt onset of RUQ pain, nausea and vomiting, the late development of fever, and RUQ tenderness on abdominal palpation, is acute partial gallstone obstruction. Furthermore, this diagnosis is supported by finding a “suspicion” of a gallstone on MRCP.

FDA adjudication of the remaining 27 patients randomized to dapagliflozin and identified by the sponsor as potential liver toxicity cases is provided in Table 2 on the following page. This table includes CDER adjudication for causality and includes 2 cases whose treatment arm remained blinded as of the date of the Hepatic Adjudication Report (14 April 2011). A brief description and assessment of each of these cases is included in this document (ADDENDUM).

Table 2. Reformulation of Table 3.1 from sponsor’s Hepatic Adjudication Review identified by the sponsor as cases of potential liver toxicity other than potential Hy’s Law severity with FDA causality.			
	Injury category	ID	Causality per CDER
Dapagliflozin treated			
9	Other Liver	D1690C00004-3104-4	Not DILI
10	Other Liver	D1690C00004-4919-3	Not DILI
11	Other Liver	D1690C00004-5419-9	Not DILI
12	Other Liver	D1690C00005-2003-3	Adaptation
13	Other Liver	D1690C00005-4010-3	Possible DILI – not dapagliflozin
14	Other Liver	D1690C00005-6032-25	Unlikely
15	Other Liver	D1690C00006-1101-10	Not DILI
16	Other Liver	D1690C00006-1219-13	Not DILI
17	Other Liver	D1690C00006-1812-18	Insufficient data
18	Other Liver	D1690C00006-2202-7	No evidence of liver injury
19	Other Liver	D1690C00006-2203-7	Not DILI
20	Other Liver	D1690C00012-304-6	Not DILI
21	Other Liver	MB102008-76-149	Not DILI
22	Other Liver	MB102013-28-542	Not DILI
23	Other Liver	MB102013-52-188	Unlikely
24	Other Liver	MB102013-87-179	Unlikely
25	Other Liver	MB102013-96-136	Unlikely
26	Other Liver	MB102014-16-11	Unlikely
27	Other Liver	MB102014-43-75	Unlikely
28	Other Liver	MB102029-4-276	Unlikely
29	Other Liver	MB102029-88-538	Not DILI
30	Other Liver	MB102029-89-338	Unlikely

31	Other Liver	MB102030-90-706	Unlikely
32	Other Liver	MB102032-67-399	Unlikely
33	Other Liver	MB102034-83-764	Unlikely
34	Other Liver	MB102-034-143-763	Not DILI
35	Other Liver	MB102-034-156-775	Not DILI
Treatment Arm Blinded			
36	Other Liver	D1690C00018-6710-4	Not DILI
37	Other Liver	D1690C00018-7835-7	Possible DILI – not dapagliflozin

DISCUSSION

After review of 37 cases of liver injury from the dapagliflozin clinical development program, it appears that based on currently available data there is one Hy’s law case in which a causal association with dapagliflozin is “Probable.” Although there are a number of cases in which information to help make a diagnosis and causality assessment is lacking, the abnormalities identified were by and large quite mild. Follow-up information with the sponsor may be useful to make a disposition concerning causality for some of these cases.

Assessing the likelihood of hepatotoxicity is a difficult problem and in general is based on identifying liver dysfunction that develops within a few days to up to six months after starting a drug that does not appear to be a result of other conditions that cause liver disease and that may mimic drug-induced liver disease (DILI). Thus it can be viewed as a “diagnosis of exclusion.” Accordingly, this requires that in clinical trials when liver injury is observed, as outlined in the CDER Guidance document, all other conditions that can mimic DILI are sought and excluded. Even after concluding that DILI is the probable cause after excluding potentially competing causes, identifying the specific drug, herbal, or dietary supplement can be challenging if, in fact, more than one or even numerous products are being received. Selecting a specific product takes into account an appropriate temporal relationship between the start of the drug and the first identification of possible liver disease (based generally on the development of increased serum enzymes or bilirubin levels or on appropriate symptoms) as well as considering the past history of the drug with regard to its potential for causing hepatotoxicity. The latter, of course, is not relevant if the drug in question is currently in development. Finally, given the fact that a diagnosis of DILI is rarely certain since there is no specific biomarker that permits a definitive diagnosis of DILI, and thus there are subjective differences in attempting to make the diagnosis, efforts have gone into developing grading systems of likelihood of the diagnosis.

For the present analysis, a major problem in regard to assessment for potential DILI for some of the cases was the paucity or complete absence of data that would permit reaching a reasonable diagnosis of the liver injury, whether DILI or another definable cause.

CONCLUSION

In total, approximately 3,000 individuals with T2DM have been exposed to dapagliflozin (2.5 mg or higher) for over 6 months and 2000 subjects were exposed to the 10 mg dose in the Phase 2b and 3 clinical program. The average duration of observation in dapagliflozin arms was 341 days and 316 days in control arms. Based on data available at this time and the size of the exposure population in the development program, one case consistent with Hy's law has been identified in association with dapagliflozin. In this review, an analysis of protocols for the monitoring of serum liver biochemistry values and study protocol adherence has not been performed. Moreover, any potential impact of study subject drop-outs and loss to follow-up has not been analyzed in this review. There are a number of other cases that lack sufficient data to link them to treatment with dapagliflozin. There are also cases of limited serum ALT elevation identified by the sponsor and assessed as probably caused by dapagliflozin by the sponsor's Independent Adjudication Committee for Adverse Hepatic Events. Although there is no imbalance in hepatic events between dapagliflozin and control arms per the sponsor's analysis (and reproduced herein in the Appendix as Tables 3 and 4), because of the importance of recognizing sentinel cases of DILI in registrational trials as outlined in the 2009 pre-marketing guidance⁸ it is prudent to gather more information on all relevant cases as part of an in-depth review of the dapagliflozin NDA in order to assess whether this agent may be hepatotoxic. As further clinical studies are performed, careful serum and clinical monitoring of dapagliflozin study subjects should be preformed to definitively determine whether this agent is associated with risk to cause clinically serious DILI.

⁸ Guidance for Industry – Drug-Induced Liver Injury: Premarketing Evaluation. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

APPENDIX

Table 3. Proportion of Subjects with Elevated Serum Aminotransferases – Short-term and Long-term Treatment Period – All Dapagliflozin Phase 2b and 3 Pool Treated Subjects. Adapted from Table 84 in Sponsor’s Summary of Clinical Safety (Report date 30-Nov-2010)		
	Dapa arms (N=4287)	Control arms (N=1941)
	n / N (%)	n / N (%)
Total subjects with “elevated liver tests” as defined by the sponsor	206 / 4258 (4.8)	85 / 1922 (4.4)
AST elevation		
> 3X ULN	38 / 4258 (0.9)	16 / 1922 (0.8)
> 5X ULN	11 / 4258 (0.3)	8 / 1922 (0.4)
> 10X ULN	5 / 4258 (0.1)	3 / 1922 (0.2)
>20X ULN	4 / 4258 (0.1)	0 / 1922 (0)
ALT elevation		
> 3X ULN	61 / 4258 (1.4)	28 / 1922 (1.5)
> 5X ULN	17 / 4258 (0.4)	9 / 1922 (0.5)
> 10X ULN	4 / 4258 (0.1)	3 / 1922 (0.2)
>20X ULN	2 / 4258 (<0.1)	1 / 1922 (0.1)
AST or ALT elevation		
> 3X ULN	73 / 4258 (1.7)	33 / 1922 (1.7)
> 5X ULN	19 / 4258 (0.4)	12 / 1922 (0.6)
> 10X ULN	5 / 4258 (0.1)	5 / 1922 (0.3)
>20X ULN	4 / 4258 (0.1)	1 / 1922 (0.1)

Table 4. Proportion of Subjects with Elevated Serum Bilirubin with and without Concurrent Elevations of Serum Aminotransferases – Short-term and Long-term Treatment Period – All Dapagliflozin Phase 2b and 3 Pool Treated Subjects. Adapted from Table 84 in Sponsor’s Summary of Clinical Safety (Report date 30-Nov-2010)

	Dapa arms (N=4287)	Control arms (N=1941)
	n / N (%)	n / N (%)
Total Bilirubin Elevation		
> 1.5X ULN	55 / 4258 (1.3)	18 / 1921 (0.9)
>2X ULN	18 / 4258 (0.4)	5 / 1921 (0.3)
AST or ALT > 3X ULN and Total Bilirubin > 1.5X ULN: window = +/- 14 days	8 / 4258 (0.2)	4 / 1921 (0.2)
AST or ALT > 3X ULN and Total Bilirubin > 2X ULN: window = +/- 14 days	5 / 4258 (0.1)	3 / 1921 (0.2)
AST or ALT > 3X ULN and Total Bilirubin > 1.5X ULN and AlkPhos < 2X ULN: window = +/- 14 days	3 / 4258 (0.1)	2 / 1921 (0.1)

ADDENDUM

D1690C0004-3104-4: 63 year man, apparently a heavy alcoholic, develops “hepatic failure” on “study day 58, 45 days after study medication was discontinued days after stopping the test drug”. He was somnolent and rectal examination revealed melena. His ALT was 794, AST 1604, and bilirubin 51 μ mol. An abdominal scan showed a markedly enlarged liver with possible metastases. He dies the next day. Autopsy: Primary small cell lung cancer with widespread liver metastases.

Comment: Not drug-induced liver injury

D1690C00004-4919-13: 71 year old man develops coagulation defect on day 16. Day 35 found to have increased AST and ALT (both 123). No bilirubin reported. Withdrawn from study because of renal failure. Sonography reported to show cirrhosis. Hepatitis markers all negative, ANA 1:320. ALT back to normal days 46 and 57.

Comment: No evidence of drug-induced liver injury. There are insufficient data to explain transient increase in ALT and AST.

D1690C0004-5419-9: 52 year old man, discontinued from study medication on day 20 because of severe abdominal pain, nausea and vomiting. No liver-related biochemical tests shown. CT scan shows evidence of liver abscess and diverticulitis; the abscess was aspirated.

Comment: Diagnosis is diverticulitis with liver abscess soon after starting study with normal baseline liver chemistries.

D1690C00005-2003-3: 70 year old female with a BMI of 29. Day 225 found to have asymptomatic elevation in liver chemistries (ALT 511, AST 940, ALP 139, bilirubin 1.5). No follow-up values reported. Hepatitis serology was said to be negative. Study drug was discontinued on day 228 for two weeks and values returned to normal. Drug started again day 245 and liver tests reported to remain normal (values not shown). No other cause for abnormalities reported.

Comment: Cause of abnormalities uncertain because of sparse data. Drug induced liver injury may be considered unlikely in view of a negative re-challenge. However, since there is no other obvious cause for the raised enzymes, and there is a temporal relationship between receipt of the drug and evidence of liver dysfunction, drug-induced liver injury cannot be completely exonerated because of the possibility of drug adaptation. Nevertheless, drug-induced liver injury is only a low possibility.

D1690C00005-4010-3: 59 year old man had a “mild” automobile accident on day 105 of study treatment. Had cervical sprain and on day 272, started on loxoprofen, eperisone, rebamipide, azelastin. Six days later developed ALT 5 x ULN. No other values reported. Investigator implicated the new medication (without specifying which one) and stopped the medications on day 277. A week later, ALT fell to 1.4 x ULN and remained at 1.1 x ULN when subject completed the study. No hepatitis or autoimmune serology reported.

Comment: Reported data insufficient to reach a definitive diagnosis for what appears to have been a transient elevation in ALT values without indicating results of other liver-related chemistries. The investigator suggests the possibility of drug-induced liver injury because of resolution of abnormal values after discontinuing the “medications for cervical sprain” without indicating which one. However, the reported incomplete data suggest that the test medication was continued without causing liver dysfunction that suggests it could not have been responsible for the liver dysfunction.

D1690C00005-6032-25: 54 year old female. No information other than that an adverse event developed that resolved when the drug was discontinued. Further, no other data supplied except for mention of an ALT of 52 and an AST of 21. Upper limits of normal not stated. Patient was hospitalized from day 35 to 44.

Comment: Data completely insufficient to reach any diagnostic conclusion. No evidence of drug-induced liver injury, however.

D1690C00006-1101-10: 70 year old man with a history of cholecystitis, status post-cholecystectomy. No laboratory data shown. Stated that “event of moderate pancreatic neoplasm started on day 85.” Hospitalized day 97. Developed RUQ pain, anorexia and weight loss; CT demonstrated tumor at head of pancreas. Study drug discontinued. Discharged from hospital day 109 not fully recovered.

Comment: Apparent diagnosis is pancreatic cancer and not drug-induced liver injury.

D1690C00006-1219-13: 63 year old obese male treated with study drug until day 138 which was discontinued because of planned elective cardiac surgery for aortic valve replacement and coronary artery bypass surgery. Had “pulmonary laceration” and developed aortic dissection. Developed acute hypotension and renal and hepatic insufficiency and died a day later. No laboratory values reported.

Comment: Diagnosis of “hepatic insufficiency” a result of apparent complications during cardiac surgery, presumably acute hypotension in addition to “cardiogenic hepatopathy.” Clearly not drug-induced liver injury.

D1690C00006-1812-18: 59 year old female with normal ALT values through 365 days of treatment, develops a spike in the ALT value to 351 (no other labs shown) on day 456 (all values before that time were normal), which falls to 75 on day 462, returning to normal on day 537, the time of next testing. She remains asymptomatic. No further information and no comment on potential etiology. Also, no mention of whether the test drug was discontinued.

Comment: There are insufficient data to draw any conclusions. If the use of the test drug was continued, the abnormality would not be attributed to the test drug.

D1690C00006-2202-7: 64 year old obese male develops increased level of serum creatinine on day 233 of treatment. Creatinine remained elevated through day 446. No liver tests reported. Patient withdrew from study.

Comment: No report of liver dysfunction and therefore not drug induced liver injury.

D1690C00006-2203-7: 59 year old obese male diagnosed with liver cancer on day 42, etiology undefined because most potential etiologies were excluded. Left study day 85 and died the same day. No laboratory values shown.

Comment: Not drug-induced liver injury.

D1690C00012-304-6: 72 year old male with COPD and numerous other pathological conditions including tachyarrhythmia, develops pneumonia on study day 64. Treated with antibiotics and low MW heparin, Develops atrial fibrillation with tachycardia. Transferred to ICU where he develops sudden massive and unmanageable upper GI bleeding and dies. Autopsy reveals a large liver but histology not reported. Varices identified. No history of liver disease. Live-related biochemical tests (not shown) reported to be normal.

Comment: Death due to massive upper GI bleeding from varices and not due to drug-induced liver injury.

MB102008-76-149: 60 year old male developed a single set of abnormal chemistries on study day 32 (ALT 346; AST 364, bilirubin 1.7, ALP 117). Values before were quite normal, the ALT remained slightly elevated on day 27, and all returned to normal thereafter. Bilirubin values were always a little elevated but fractionated values were not reported so it is unknown whether the patient had Gilbert's disease. Treatment was not discontinued.

Comment: Data reported insufficient to establish cause for sudden transient increase in aminotransferase levels. Could conceivably be a mix-up in blood sample. No etiology advanced. Presumably not drug-induced liver injury.

MB102013-28-542: 43 year old male develops a dramatic increase in CPK and an AST of 229 on day 115, the values returning to normal at the next testing, day 124. Worked up for an MI that was ruled out. Was not on any other pertinent medication and had no muscle cramping or pain. Was this also a miss-labeled blood sample?

Comment: Diagnosis unknown but not drug-induced liver injury.

MB102013-52-188: 32 year old female with mild liver test abnormalities present before starting the study (ALT 99, AST 62, ALP 89, Bili 0.4). Similarly at baseline, abnormalities were present in the same range (ALT 92, AST 34, ALP 89, Bili 0.5). No explanation offered for the cause of these persisting abnormalities including no hepatitis serology. On day 110, the ALT increases into the 100s (ALT 124) with a slight increase in the AST from baseline (AST 52). Thereafter, the ALT value fluctuates but remains well above 100, increasing to 190 with an AST value of 82 on day 536, peaking on day 551 at an ALT of 273. At no time was there an increase in serum bilirubin. The drug was discontinued on day 563 and the last value recorded for the ALT on day 564 was 239. Incredibly, no information is provided with regard to the etiology of the persisting liver dysfunction – could this be, for example, chronic hepatitis C? One might wonder why this patient with abnormalities to begin with, was entered into this trial.

Comment: Clearly this patient had pre-existing chronic liver disease of undetermined etiology. The late doubling of the ALT value also remains undetermined; conceivably it might be a consequence of a flare of the underlying chronic liver disease or perhaps worsening as a result of the drug. Hepatitis serology is clearly needed. In my view, this is more likely to be a flare of underlying chronic liver disease, but superimposed acute drug injury cannot be entirely excluded in the absence of additional information. Still, I would consider drug induced liver injury superimposed upon underlying chronic liver disease a very low possibility

MB102013-87-179: 53 year old female develops a sudden elevation in the aminotransferases values (actual value not reported but graphic display indicates that the ALT increased to a little over 300 and the AST increased to approximately 150), falling considerably when tested 10 days later and then shortly thereafter, returning to normal. Study drug was discontinued on day 176 and then re-started on day 183 but no further abnormalities developed despite apparent continued treatment (description difficult to understand).

Comment: Cause for the sudden transient increase in serum aminotransferase values not apparent because either it was not sought or simply not commented upon. The likelihood

of drug-induced liver injury is remote to unlikely given the fact that r-challenge did not recreate the abnormality.

MB102013-96-136: 58 year old female who started with a slight increase in the ALP level (161), a slight increase in the ALT (60) and normal AST and bilirubin values. On day 265, there was a single increase in values (ALT 107, AST 45 with normal ALP and bilirubin) that was back to normal at the next reported testing, day 351. On day 628, a second increase occurred (ALT 200, AST 156, ALP 135, bilirubin 1.3), the ALT returning to near normal on day 631. There were no associated symptoms. The drug was withheld for 3 days and on observing the reduction in the ALT, was re-started and continued until day 720 without further elevations.

Comment: Like the previous case, the cause for a single increase in liver tests remains unclear, but in the absence of evidence of recurrence of abnormalities with re-challenge, drug induced liver injury is unlikely.

MB102014-16-11: 55 year old female with pre-treatment elevated ALT of 50 (AST 35), and baseline ALT of 99 (AST 62). The patient continued to have persistent mild and fluctuating elevations in ALT and occasionally in AST. The drug was stopped on day 43 because of very slight worsening of the ALT value. No cause for these abnormalities is offered. No comment of whether screening was performed for viral hepatitis or AIH serology.

Comment: Precise cause for persistent ALT elevation unknown – could this be fatty liver disease? Almost certainly not drug-induced liver injury.

MB102014-43-75: 56 year old female with slightly elevated ALT and AST at baseline. First test reported is at day 148 when her ALT is 230, AST 120 with no other data reported. No report of seeking hepatitis or AIH serologies. Raised serum enzymes, particularly ALT, persist until day 184. The next set of values is on day 260 when enzymes are normal. No data reported on serum bilirubin. Patient is on multiple drugs.

Comment: Cause of abnormalities completely unknown; no evidence of workup for etiology. Therefore, until a definitive etiology can be identified, drug induced liver injury cannot be completely excluded. Thus, drug-induced liver injury a low possibility.

MB102029-4-276: 83 year old man with a complicated medical history. Patient started with normal liver chemistries until day 173 of treatment when he was found to have an ALT of 419, an AST of 355, an ALP of 355 and a serum bilirubin of 1.0 (double the earlier values). By day 175, his ALT was 444, AST 320, ALP 410, and bilirubin 1.0. The next set of values, on day 197, showed a marked reduction in both aminotransferase values (both down to 63) but an increase in both the ALP, to 445, and the bilirubin, to

8.9. Thereafter, the aminotransferases stayed at a moderately increased level but the ALP and bilirubin remained quite elevated finally returning to normal by day 372, following which aminotransferases showed fluctuating increases, staying abnormal until the last value reported; this suggests possible evolution to chronic hepatitis. The patient was without symptoms when the event began. The test drug as well as pravastatin and nicotinic acid were discontinued when the first abnormalities were noted. Serologic tests for hepatitis A, B and C were all negative. The obstructive pattern of liver chemistries obviously prompted evaluation for causes of obstructive jaundice. Ultrasonography demonstrated slight hepatomegaly. An MRI showed intra-hepatic duct dilatation with normal sized common bile duct and no obvious mass. An ERCP was then performed showing stricture of the common hepatic duct at the bifurcation suggestive of cholangiosarcoma. Cytologic brushings, however, were negative for malignancy. He had an elevated CA-19.9 and an elevated CEA. On day 276, patient developed a urinary tract infection and on day 277, developed acute congestive failure as a consequence of an acute MI. The patient was said to be stable but the last value reported shows a second increase in the AP from a previous level of 132 to 404 and an increase in bilirubin from 0.7 to 2.9. The narrative does not mention this.

Comment: The overall data regarding liver disease points to an obstructive pattern, most likely some cause for extrahepatic obstruction. The earlier return to normal values had lowered the likelihood of a malignancy, but the apparent recurrence of obstruction at the last report is disturbing and once again raises the possibility of a malignant process. Drug induced liver injury seems unlikely.

MB102029-88-538: 62 year old female. Extremely short narrative does not mention abnormal liver chemistries or any evidence for liver disease whatsoever. Only issue reported is painful defecation and abdominal pain.

Comment: Not drug-induced liver injury.

MB102029-89-338: 77 year old female with initial normal liver chemistries develops an ALT value of 212 on day 156, falling to 106 on day 167, to 88 on day 170, returning to normal on day 199. Other than ALP value that remained normal throughout, no other values are shown although there is mention of a normal AST value on the first day of an abnormal ALT. No mention of a specific evaluation of the abnormality. Study medication was discontinued on day 165 and was re-started on day 170. Thereafter, serum enzymes remained normal suggesting a negative re-challenge.

Comment: Information too sparse to define etiology. However, drug-induced liver injury seems unlikely in view of a negative re-challenge.

MB102030-90-706: 60 year old white female treated with test drug. Two weeks before starting treatment and for 259 day while on treatment, the patients had completely normal

liver-related biochemical tests. On day 345 of treatment, she is reported to have developed upper abdominal pain and “cholelithiasis.” At the same time, she was found to have liver test abnormalities: ALT 805, AST 941, ALP 306, bilirubin 1.4. Follow-up on day 351, representing the only additional set of chemistries, displays an ALT of 102, a normal AST value (20) and a normal bilirubin value (0.3) with a falling ALP (170). Absolutely no other information is supplied (i.e. no viral hepatitis and AIH serology, the absence or presence of fever and/or leucocytosis, imaging studies for potential gall stones in the gallbladder or dilated bile ducts, a history of cholelithiasis, etc.). Also, no information is presented regarding whether or not the test medication was discontinued and what other drugs might have been given the patient. Therefore, a potential diagnosis has to be inferred on the background of extremely skimpy data.

Comment: Based on data made available, I infer that the patient’s abnormal liver chemistries were probably due to biliary tree disease, perhaps the passing of a gallstone, based on a history of upper abdominal pain, the development of relatively short-lived serum enzyme elevations, particularly of the ALP, the slight elevation of serum bilirubin, and the fact that the patient’s upper abdominal pain resolved 2 days after its initiation. I think that, despite the lack of serologic markers, it is unlikely that viral hepatitis or autoimmune hepatitis were responsible for this short lived abnormality. I believe that drug induced liver injury is unlikely.

MB102031-67-399: 50 year old female from India develops an ALT of 224, an AST of 165, and ALP of 223 with a normal serum bilirubin on day 14 of study treatment. The test drug was withheld on day 19. On day 20, the ALT is 82 and the AST is near normal. All values return to normal by day 26. Tests for hepatitis B and C were negative. The patient had developed fever, weakness and myalgias and a chest X-ray revealed findings suggestive of TB. The test drug was restarted on day 25 and treatment for TB was begun. Despite continued treatment with the test drug, serum enzymes remained normal.

Comment: Unclear what the cause was for the transient biochemical dysfunction but may somehow be related to the acute onset of TB. Given the fact of a negative re-challenge with the study drug, drug-induced liver injury is unlikely.

MB102034-83-764: 47 year old female with a past history of abnormal amino-transferases and which are slightly abnormal up to the time of starting study drug. However, they are normal as the study begins, the ALT rising to 52 and the AST rising to 48 on day 15. Serum bilirubin values are normal. On day 32, ALT is now 112 and the AST is 165 with a normal bilirubin, The next and last set of values reported, on day 43, still show abnormal values for ALT and AST although a little less so. The investigator therefore stops medication on day 57. No further information.

Comment: The basis for the pre-existing abnormal chemistries is not reported and could be a result of fatty liver disease or treatment with statins. The cause for the later abnormalities is also not defined and there are no follow-up data to determine whether

withdrawal of the drug was followed by dechallenge. Too little information supplied to define the cause for the abnormalities, but drug induced liver injury cannot be entirely excluded.

MB102034-143-763: 46 year old male with normal bilirubin value prior to starting treatment. On day 1, his bilirubin level was found to be 2.1 with all serum enzymes normal. Bilirubin not fractionated. Patient had no symptoms. Screening serologies for hepatitis B and C all negative. Treatment was discontinued on day, stated to be “due to the event.” Bilirubin said to normalize on day 6.

Comment: Not drug induced liver injury. Patient presumably has Gilbert’s syndrome.

MB102034-156-775: 52 year old female had mild elevation of serum enzymes at baseline (ALT 49, AST 40, ALP 137). During treatment, developed fever, vomiting, cramps and diarrhea on day 27; no changes in liver chemistries at the time. Admitted to the hospital diagnosed as gastroenteritis and dehydration. Given IV fluids and anti-emetics and was discharged from hospital within 24 hours. Diarrhea resolved day 38. Baseline hepatitis B and C both negative. Slight increase in serum enzymes occurred on day 59 (ALT 68, AST 110 with normal ALP and bilirubin). Levels back to normal 1 week later but study drug discontinued on day 63. Patient was receiving a statin drug.

Comment: No etiology for abnormal aminotransferases (mostly mild) offered. This is not drug induced liver injury. Could be due to statin use or fatty liver disease.

D1690C00018-6710-94 (Blinded to treatment arm): 66 year old man started with normal liver panel tests (ALT 15, AST 15, bili 9 µmols, ALP 84). At visit 5 (1 week after starting drug), ALT 687, AST 341, ALP 173, LDH 285, bili 10 µmols. Patient had no symptoms. Three days later, ALT 267, AST 71, AP 155, bili 15 µmols. Tests for hepatitis A, B, C and EBV all negative as were the AIH markers. Baseline test for HEV negative but HEV IgM was positive on July 13 suggesting that the patient had developed acute hepatitis E infection. Study drug was not interrupted.

Comment: Patient did not have drug induced liver injury but appears to have developed acute hepatitis E. Strangely, this diagnosis was not acknowledged in the case summary.

D1690C00018-7835-07 (Blinded to treatment arm): 55 year old female. Baseline liver chemistries all normal. At visit 7, approximately 2 months after starting study drug, was found to have an ALT of 283, an AST of 288, an ALP of 102 and a normal serum bilirubin value. A week later, her ALT was 192, her AST 80, ALP 120. A week beyond that, her values were still elevated but all returned to normal a week after that and remained normal. Hepatitis serology, A, B, C and EBV were all negative. Results pending were for HEV and AIH markers. The study drug was discontinued when

abnormalities were noted and was re-started about 4 months later without apparent adverse effect on the liver.

The investigator was uncertain of the diagnosis but suggested that it might have been a reaction to azithromycin that was administered because of an URI.

Comment: Drug induced liver injury due to the study drug unlikely but may possibly be due to azithromycin. No recurrence when study drug was re-started.

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/s/

ALLEN D BRINKER
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
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Date: June 2, 2011

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Subject: Review of the published literature and the sponsor's epidemiological study entitled "A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population."

Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-1476

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EXECUTIVE SUMMARY

As background information for an upcoming Advisory Committee meeting for the New Drug Application (NDA) of dapagliflozin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE) to provide information on the background incidence rate of breast cancer among type 2 diabetes patients.

Nine cases of breast cancer have been observed in the dapagliflozin treatment groups versus none in the comparator groups in dapagliflozin clinical trials. The epidemiologic literature was reviewed to evaluate the background incidence rate of breast cancer among type 2 diabetes patients. A study report conducted by the sponsor titled “A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population” was also reviewed.

A total of 6 studies (3 prospective and 3 retrospective cohort studies) that contained quantifiable incidence estimates were included in this review. The reported incidence rates of breast cancer among diabetes patients (mostly type 2 diabetes) ranged from 0.62 to 4.04 per 1,000 person-years of follow-up. The U.S. female type 2 diabetes patients were found to have the highest incidence rates of breast cancer, which were 4.04 and 3.41 per 1,000 person-years in two studies. Second to the U.S. females, the Canada postmenopausal women with newly diagnosed type 2 diabetes had incidence rates of 3.02 and 2.90 per 1,000 person-years for those who were 65 years and older, and those between 55 and 65 years, respectively. Two studies conducted in Sweden reported that the incidence rates of breast cancer in type 2 diabetes patients were 2.44 and 1.67 per 1,000 person-years for females, and 0.03 and 0.02 per 1,000 person-years for males. The Japanese women were reported with the lowest incidence rate of breast cancer at 0.62 per 1,000 person-years. Compared to the reported incidence rates of breast cancer among type 2 diabetes patients in the literature, the age-specific incidence rates of breast cancer were consistently higher in the dapagliflozin clinical trial program.

The sponsor used age- and sex-specific incidence rates of breast cancer data from the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) program to calculate the expected number of breast cancer cases in the dapagliflozin clinical trials. A standardized incidence ratio (SIR) was calculated to evaluate the observed incidence of breast cancer for the female cohort of the dapagliflozin clinical program compared to the expected incidence from SEER estimates. An adjustment factor of 20% increased risk of breast cancer in type 2 diabetes was applied and 95% confidence intervals were calculated for the SIR. The adjusted total number of expected incident breast

cancer cases among female patients exposed to dapagliflozin was 7.1. The calculated SIR was 1.27 (95% CI, 0.58-2.41) for dapagliflozin-treated patients. The adjusted total number of expected incident breast cancer cases among female patients in the comparator arms was 2.9.

There is insufficient evidence to support the sponsor's statement that the results provide some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age. The expected number of cases in the comparator arms was 2.9. However, no case was observed in the comparator arms of the dapagliflozin clinical program. This finding suggests that the study participants in the dapagliflozin clinical program may have a lower risk of breast cancer compared to the general type 2 diabetes population of the same age. However, the number of observed breast cancer cases (n=9) in the dapagliflozin trials were more than the expected number of cases (n=7.1) in the dapagliflozin-treated arms. One possible explanation to this finding is that dapagliflozin treatment may be associated with an increased risk of breast cancer. The application of a 20% diabetic risk adjustment factor to SEER data may have overestimated the expected number of cases to be seen in the dapagliflozin clinical trials because some patients in SEER were actually diabetes patients. The overestimated expected number of cases would have resulted in an underestimated SIR. Another limitation of using SEER data is that the dapagliflozin clinical trials were conducted internationally and the U.S. represented with approximately 20% of the total trial population. As rates of breast cancer vary across countries, the estimates from SEER (U.S. data) could be biased. With those limitations and concerns, we can not be reassured that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age.

In summary, the finding that the age-specific incidence rates of breast cancer were higher than those reported in the literature could be a safety signal that dapagliflozin may be associated with an increased risk of breast cancer. The SIR calculated by the sponsor using SEER data as an external reference group is not reassuring due to the study limitations. It is not feasible to establish the relative risk with any degree of certainty at this time given the small number of events (9 cases in the dapagliflozin treatment groups and zero in the comparator groups) and a wide confidence interval for the incidence rate ratio that includes 1.0 and infinity. Therefore, it is uncertain whether dapagliflozin treatment is associated with an increased risk of breast cancer. Continued follow-up of all participants in the dapagliflozin trials for breast cancer and further analysis with a direct comparison between the dapagliflozin treatment arms

and the comparator arms should be conducted to evaluate the relative risk of breast cancer associated with dapagliflozin treatment.

1 INTRODUCTION

As background information for an upcoming Advisory Committee meeting for the New Drug Application (NDA) of dapagliflozin, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE) to provide information on the background incidence rate of breast cancer among type 2 diabetes patients.

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose co-transporter, the major transporter responsible for renal glucose reabsorption. This new molecular entity (NME) is currently undergoing NDA review as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin lowers both fasting and postprandial plasma glucose by inhibiting the renal reabsorption of glucose and by promoting its urinary excretion. The dapagliflozin sponsors are Bristol-Myers Squibb and AstraZeneca.

Nine cases of breast cancer were observed in the female dapagliflozin-treated patients versus none in the comparator arms of the dapagliflozin clinical trials. The epidemiologic literature was reviewed to evaluate the background incidence rate of breast cancer among type 2 diabetes patients. A study report conducted by the sponsor titled “A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population” was also reviewed.

2 METHODS AND MATERIALS REVIEWED

2.1 LITERATURE

A systematic literature search was conducted in PubMed for publications in English language published through May 23, 2011. The keywords used in this search were (“incidence of breast cancer” OR “risk of breast cancer”) AND “diabetes”.

All abstracts were reviewed for study design and relevance to this review. Case reports and review studies were excluded from this review because they did not contain population-based or original breast cancer risk estimates. Studies that estimated incidence rates of breast cancer among patients with type 1 diabetes were also excluded. The full text of observational cohort studies and studies that were

referenced in a meta-analysis of breast cancer risk associated with diabetes were reviewed. Studies that contained breast cancer incidence estimates were included in this literature review.

2.2 SPONSOR'S STUDY REPORT

A study report conducted by the sponsor titled "A comparison of the incidence of breast cancer in the dapagliflozin clinical program with the incidence of breast cancer in a reference US population" was also reviewed.

3 RESULTS & DISCUSSION

3.1 LITERATURE

After screening the medical literature for relevant information to quantify incidence rate of breast cancer among type 2 diabetes, a total of six studies that contained quantifiable incidence estimates were selected, which included three prospective cohort and three retrospective cohort studies (Table 1). Two studies each were conducted in the U.S. and Sweden, and one each was conducted in Canada and Japan.

The reported incidence rates of breast cancer among diabetes patients (mostly type 2 diabetes) ranged from 0.62 to 4.04 per 1,000 person-years of follow-up. The U.S. female patients were found to have the highest incidence rates of breast cancer, which were 4.04 and 3.41 per 1,000 person-years in two studies. Second to the U.S. females, the Canada postmenopausal women with newly diagnosed type 2 diabetes had incidence rates of 3.02 and 2.90 per 1,000 person-years for those who were 65 years and older, and those between 55 and 65 years, respectively. Two studies from Sweden reported that the incidence rates of breast cancer were 2.44 and 1.67 per 1,000 person-years for females, and 0.03 and 0.02 per 1,000 person-years for males. The Japanese women were reported with the lowest incidence rate of breast cancer at 0.62 per 1,000 person-years.

3.1.1 Study Summaries & DEPI Comments

3.1.1.1 Study Summary

Mink et al¹. examined the incidence of breast cancer in a cohort of women aged 45-64 years at baseline during 1987-1989 from four U.S. communities in Minnesota, North Carolina, Maryland, and Mississippi. Incidence breast cancers diagnosed between January 1, 1987 and December 31, 1995 were ascertained by linkage to a cancer registry and/or medical record review of potential cases identified through annual telephone follow-up surveys. Patients with a history of cancer at baseline were excluded.

Person-years at risk were calculated for each participant as time between the baseline examination date and December 31, 1995, or the date of breast cancer diagnosis, death, or loss to follow-up, whichever occurred first. The incidence of breast cancer was 4.04 per 1,000 person-years among those women with newly diagnosed type 2 diabetes over an average follow-up period of 7.1 years.

3.1.1.2 Comments

Since the study subjects were from four U.S. communities, they were not nationally representative. The study results cannot be generalized to the U.S. population.

3.1.1.3 Study Summary

Another U.S. study conducted by Michels et al². reported an incidence rate of invasive breast cancer of 3.41 per 1,000 person-years among female nurses who were 30-55 years old and free of cancer in 1976 over 22 years of follow-up period. Participants were followed from 1976 through 1996 for the occurrence of type 2 diabetes and through 1998 for subsequent invasive breast cancer. Cases of breast carcinoma in situ (n=612) and ductal carcinoma in situ were censored from the analysis. Twenty nine cases of breast cancer that developed during follow-up period were excluded because the dates of diagnosis were not available.

3.1.1.4 Comments

The incidence rate in this study was under-estimated since cases of breast carcinoma in situ, ductal carcinoma in situ, and cases of breast cancer without dates of diagnosis were excluded. A fraction of the breast carcinoma in situ may progress to become invasive and some of the cases without dates of diagnosis may be subsequent incidence cases of breast cancer after the development of type 2 diabetes.

3.1.1.5 Study Summary

Lipscombe et al³. conducted a retrospective population-based cohort study to examine the incidence of invasive breast cancer among postmenopausal women aged 55-79 years with newly diagnosed diabetes between April 1, 1994 and March 31, 2002 in Canada. Women with a history of breast cancer, those who developed breast cancer within the first year of study entry, who died, moved out from the province, or became 80 years of age within the first year were excluded. Follow-up began at the date of the first diabetes diagnosis. During the median follow-up period of 4.5 years, 451 and 560 breast cancer cases were identified in women age 55-65 years (2.90 per 1,000 person-years) and ≥65 years (3.02 per 1,000 person-years), respectively, in the Ontario Cancer Registry. The registry relies on

four sources for data: hospital discharge summaries, pathology reports, clinical records from cancer centers, and death certificates.

3.1.1.6 Comments

The estimated incidence of invasive breast cancer may be underestimated because women who developed breast cancer (n=308) within the first year after the diagnosis of diabetes were excluded, which was an approach to minimize detection bias. However, some of those cases may be true incidence cases and should be included in the incidence analysis.

3.1.1.7 Study Summary

Weiderpass et al⁴. conducted a retrospective cohort study to assess the incidence of breast cancer among patients who had at least one hospital discharge diagnosis of diabetes in 1965-1983 in Sweden. The person-time of observation was from the date of discharge from the first recorded hospitalization with a diabetes diagnosis until diagnosis of breast cancer, emigration, death, or end of follow-up period (December 31, 1989). The breast cancer cases (194 women and 2 men) detected within the first year of follow-up and corresponding person-years were excluded from the incidence analysis. Cases diagnosed incidentally at autopsy were also excluded (n=21). The incidence rate of breast cancer reported in this study was 2.44 and 0.03 per 1,000 person-years for women and men, respectively.

3.1.1.8 Comments

This study probably underestimated the incidence rate of breast cancer among type 1 and 2 diabetes patients who had at least one hospitalization for diabetes. As the follow-up started from the date of hospital discharge, patients may have had diabetes for a while before their hospitalizations. Therefore, the exclusion of breast cancer cases detected within the first year of follow-up was not appropriate as many of those cases could have been incident cases.

Most diabetic patients do not require hospitalizations unless they have severe complications. Therefore, this study population had more severe diabetes because those patients had at least one hospitalization for diabetes. Since this is a non-representative sample of the diabetic population, the results for breast cancer incidence would only be applicable to patients requiring hospitalizations for diabetes.

3.1.1.9 Study Summary

Another study conducted in the same patient population in Sweden by Adami et al⁵. ended the follow-up period on December 31, 1984 instead of December 31, 1989 as in the Weiderpass study. The study design is the same as the Weiderpass study, which is a retrospective cohort study to assess the incidence of breast cancer among patients who had at least one hospital discharge diagnosis of diabetes in 1965-1983 in Sweden. The person-time of observation was from the date of discharge from the first recorded hospitalization with a diabetes diagnosis until diagnosis of breast cancer, emigration, death, or end of follow-up period (December 31, 1984). The breast cancer cases detected within the first year of follow-up and corresponding person-years were excluded from the incidence analysis. This study reported that the incidence rates of breast cancer were 1.67 and 0.02 per 1,000 person-years in women and men, respectively.

3.1.1.10 Comments

Similar to the Weiderpass study, this study probably underestimated the incidence rate of breast cancer among type 1 and 2 diabetes patients who had at least one hospitalization for diabetes. As the follow-up started from the date of hospital discharge, patients may have had diabetes for a while before their hospitalizations. Therefore, the exclusion of breast cancer cases detected within the first year of follow-up was not appropriate as many of those cases could have been incidence cases. Since the study population had more severe diabetes because those patients had at least one hospitalization for diabetes, the incidence rate is unlikely to be the same for the general diabetes population who do not always require hospitalizations.

3.1.1.11 Study Summary

A prospective cohort study conducted by Inoue et al⁶. examined the incidence rate of breast cancer among Japanese persons aged 40 to 69 years who responded to a baseline questionnaire from January 1990 to December 1994. The person-years in the follow-up started from the date of the baseline survey until the date of cancer diagnosis, emigration from the study area, death, or the end of the study period of December 31, 2003, whichever came first. The incidence rate of breast cancer among women with self-reported diabetes (type 1 and 2) was 0.6 per 1,000 person-years.

3.1.1.12 Comments

The incidence of breast cancer in this study was probably underestimated. This study obtained information on history of diabetes and history of cancer through the baseline questionnaire and the follow-up started from the date of the baseline survey. All subjects with a history of cancer at baseline (n=2219) were excluded. However, some of these cancer patients may have been incident cases of breast cancer with a history of diabetes.

Table 1. Reported incidence rates of breast cancer among type 2 diabetes patients in the literature

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
Lipscombe 2006 Retrospective Cohort	4/1/1994 – 3/31/2002	4/1/1995 – 12/31/ 2002. Median duration of follow-up: 4.5 years	Postmenopausal women (55-79 years) with newly diagnosed diabetes (vast majority were type 2 diabetes)	Canada	Female 55-65	31,142	155,311	451	2.90	Invasive breast cancer cases only. Women with a history of breast cancer, those who developed breast cancer within the first year of study entry, who died, moved out from the province, or became 80 years of age within the first year were excluded.
					Female ≥65	42,654	185,152	560	3.02	
Inoue 2006 Prospective cohort	Not available	Through 2003	Aged 40 to 69 years who responded to the baseline questionnaire between 1990 and 1994	Japan	Female		16,246.7	10	0.62	Diabetes status was self-reported and included both type 1 and 2. Diabetes Patients with a history of cancer were excluded.
Michels 2003 Prospective cohort	1976- 1996	1976-1998. Over 22 years of follow-up	Female nurses aged 30-55 and free of cancer in 1976	U.S.	Female		59,171	202	3.41	Invasive breast cancer cases only. Cases of breast carcinoma in situ (n=162) were excluded to minimize detection bias. 29 cases of newly developed breast cancer cases were excluded as the dates of diagnosis were not available.

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
Mink 2002 Prospective cohort	1987- 1995	1/1/1987 – 12/31/1995. Follow-up ended on 12/31/1995.	Women aged 45- 64 years with newly diagnosis of type 2 diabetes from Minnesota, North Carolina, Maryland, Mississippi	U.S.	Female		6,436	26	4.04	Patients with a history of cancer were excluded.
Weiderpass 1997 Retrospective cohort	1965- 1983	Up to 12/31, 1989. Mean duration of follow-up 6.7 years	Patients with at least 1 hospital admission with a discharge diagnosis of diabetes	Sweden	Female	70,110	468,497	1145	2.44	Both type 1 and 2 diabetes patients were included. 194 female and 2 male cases diagnosed during the first year of follow-up and corresponding person-years were excluded assuming those cases were prevalence at cohort entry and possibly diagnosed as ascertainment bias. 21 cases diagnosed at autopsy were excluded.
					Male	63,988	432,650	13	0.03	
Adami 1991 Retrospective cohort	1965- 1983	Through 1984	Patients with at least one hospital discharge diagnosis of	Sweden	Female	27,862	143,618	240	1.67	Both type 1 and 2 diabetes patients were included. The person- years that elapsed in

Author Year Study design	Time of diabetes diagnosis	Time of outcome identification/ Follow-up time	Study population	Study country	Gender /Age	Number of Patients	Person- years of follow- up	Number of Cases	Incidence of breast cancer per 1,000 person- years	Comments
			diabetes		Male	23,146	119,643	2	0.02	the first year of follow-up and cases detected during the same period were excluded to minimize the ascertainment bias.

3.1.2 Discussion of Literature Findings

As shown in Table 2, compared to the reported incidence rates of breast cancer among female type 2 diabetes patients in the literature, the age-specific incidence rate of breast cancer were consistently higher in the dapagliflozin clinical trial program. However, this finding should not be interpreted as dapagliflozin treatment is associated with increased risk of breast cancer. Definitions and diagnoses of breast cancer varied and there were differences in study populations by country, calendar time, patient age, and other risk factors. The breast cancer identified in the dapagliflozin clinical trials included all cases of breast cancer irrespective of grade or stage, while only invasive breast cancer was included in Lipscombe and Michels' studies.

Table 2. Female age-specific incidence rate of breast cancer in the dapagliflozin clinical trials compared with those reported in the literature

Age	Study	Incidence rate of breast cancer per 1,000 person-years	
		Literature	Dapagliflozin clinical trials *
55-64	Lipscombe (Canada)	2.90	5.73
65-79		3.02	7.15
40-69	Inoue (Japan)	0.62	3.87
50-75	Michels (U.S)	3.41	4.98
45-64	Mink (U.S)	4.04	4.11

* Calculated by DEPI based on the data from the dapagliflozin clinical trials

3.2 SPONSOR'S STUDY REPORT

3.2.1 Study Summary

The sponsor used age- and sex-specific incidence rates of breast cancer data from the Surveillance Epidemiology and End Results (SEER) program to calculate the expected number of breast cancer cases in the dapagliflozin clinical trials. Since SEER data provide incidence rates in the general population, an adjustment factor of 20% was applied to calculate the incidence rates of breast cancer in patients with type 2 diabetes based on findings from a meta-analysis⁷ that women with type 2 diabetes have a 20% increased risk of breast cancer compared to women without type 2 diabetes.

A standardized incidence ratio (SIR) was calculated to evaluate the observed incidence of breast cancer in the female cohort of the dapagliflozin clinical program compared to the expected incidence in

a population without dapagliflozin treatment. The age- and sex-specific person-time of the dapagliflozin-treated patients was multiplied by the age- and sex-specific incidence rates of breast cancer in the SEER population. The number of expected cases was calculated for each age- and sex-stratum. Those stratum-specific expected number of cases were summed to provide the total expected number of cases in the dapagliflozin-treated population. An adjustment factor for the 20% increased risk of breast cancer in type 2 diabetes was applied and 95% confidence intervals were calculated for SIR. The same analyses were conducted for female patients in the comparator arms of the dapagliflozin clinical program.

The total number of expected incident breast cancer cases among female patients exposed to dapagliflozin was 7.1. The calculated SIR was 1.27 (95% CI, 0.58-2.41) for dapagliflozin-treated patients. The total number of expected incident breast cancer cases among female patients in the comparator arms was 2.9. An SIR was not calculated for the comparator group because no incident breast cancer cases were reported in the female comparator patients of the dapagliflozin clinical trials.

The sponsor stated that the results provided some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within what one would expect for a similar population of untreated females with type 2 diabetes of the same age.

3.2.2 Comments

The use of external data source (SEER) as the reference population to evaluate the risk of breast cancer associated with dapagliflozin treatment has important limitations. The dapagliflozin clinical trials were conducted internationally and the U.S. represented with approximately 20% of the total trial population. As rates of breast cancer vary across countries, the estimates from SEER (U.S. data) could not be applicable to the international study subjects. The breast cancer identified in the dapagliflozin clinical trials included all cases of breast cancer irrespective of grade or stage, while only invasive breast cancer was included in SEER. The background incidence rates of breast cancer estimated from the SEER data are for the general population in the U.S, but not the type 2 diabetes population. Even with the adjustment factor to obtain the incidence rate of breast cancer in type 2 diabetes patients from SEER data, the patient population is different from those included in the dapagliflozin clinical trials. With the strict inclusion and exclusion criteria used in the dapagliflozin clinical program, the trial participants would be expected to be healthier than the general type 2 diabetes population. For example, patients with BMIs greater than 45 kg/m² were excluded from the dapagliflozin clinical trials. However, obesity is positively associated with both type 2 diabetes and breast cancer. Therefore, the incidence rate of

breast cancer in the general type 2 diabetes patient population in SEER should be higher than that in the dapagliflozin clinical trials. Thus using expected number of cases based on the background incidence rate of breast cancer from SEER, the calculated SIR could be underestimated.

The application of 20% increased risk of breast cancer for type 2 diabetes patients compared to non-diabetic patients to the estimated expected number of cases from SEER overestimated the expected number of cases to be seen in the dapagliflozin clinical trials. Since some patients in SEER are actually diabetes patients and the 20% diabetic risk adjustment factor should not be applied to those patients. With the over-estimated expected number of cases, the SIR may be under-estimated. Another concern is that it is unknown whether the 20% increased risk is constant across all age groups.

The expected number of cases in the comparator arms was 2.9. However, no case was observed in the comparator arms of the dapagliflozin clinical program. This finding suggests that the study participants in the dapagliflozin clinical program have a lower risk of breast cancer compared to the general type 2 diabetes population of the same age. One possible explanation is that the participants in the dapagliflozin trials are healthier because of the inclusion and exclusion criteria. According to this logic, the number of observed breast cancer cases in the dapagliflozin-treated arms should be fewer than the expected number of cases. However, the number of observed breast cancer cases (n=9) in the dapagliflozin trials were more than the expected number of cases (n=7.1) based on SEER data. One possible explanation to this finding is that dapagliflozin treatment may be associated with increased risk of breast cancer.

Based on the SIR of 1.27 (95% CI, 0.58-2.41), the sponsor concluded that the results provide some measure of reassurance that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age. However, this reviewer disagrees with the sponsor's conclusion. First of all, the few number of cases (n=9) resulted in wide confidence intervals. Secondly, the SIR may be under-estimated due to the limitations discussed above. Thirdly, the excess number of cases observed over expected in the dapagliflozin-treated patients in a potentially healthier type 2 diabetes population suggests that dapagliflozin treatment may be associated with increased risk of breast cancer. Without evaluating the relative risk of breast cancer with an internal reference group (e.g. the placebo arm) and with the study limitations, we can not be reassured that the observed incidence of breast cancer in the dapagliflozin clinical program is within the expected range for a similar population of untreated females with type 2 diabetes of the same age.

4 CONCLUSIONS & RECOMMENDATIONS

Although the ideal reference population to evaluate the relative risk of breast cancer associated with dapagliflozin treatment are patients in the comparator arms of the dapagliflozin trials as those patients are expected to have similar characteristics to those in the dapagliflozin treatment arms because of randomization, it is not feasible to establish the relative risk with any degree of certainty at this time. With nine cases of breast cancer observed in the female dapagliflozin-treated patients versus none in the comparator arms of the dapagliflozin clinical trials, it is technically not feasible to estimate the incidence rate ratio with the denominator of zero as no cases was observed in the control groups of the dapagliflozin clinical trials.

The finding that the age-specific incidence rates of breast cancer were higher than those reported in the literature could be a safety signal that dapagliflozin may be associated with an increased risk of breast cancer. The SIR calculated by the sponsor using SEER data as an external reference group may be underestimated and is not reassuring due to study limitations.

It is uncertain whether dapagliflozin treatment is associated with an increased risk of breast cancer with the current available data. Continued follow-up of all participants in the dapagliflozin clinical trials for breast cancer and further analysis with a direct comparison between the dapagliflozin treatment arms and the comparator arms should be done to evaluate the relative risk of breast cancer associated with dapagliflozin treatment.

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**Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 6/7/2011

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Subject: Incidence of Bladder Cancer in a Diabetic Population

Drug Name(s): Dapagliflozin

Submission Number: n/a

Application Type/Number: IND 068652
NDA 202293

Applicant/sponsor: Bristol-Myers Squibb and AstraZeneca

OSE RCM #: 2011-1476

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EXECUTIVE SUMMARY

The sponsor of dapagliflozin (NDA 202293, Bristol-Myers Squibb and AstraZeneca) reported 10 cases of bladder cancer in male subjects in the phase 2b and phase 3 clinical trial program. Nine of these cases occurred in the active treatment arm and one with placebo. Concerns about an imbalance in risk for bladder cancer led the Division of Metabolism and Endocrinology Products to request from the Division of Epidemiology I information on the background rate of bladder cancer in the diabetic population.

For this review, incidence rates of bladder cancer in the US general population were extracted from the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute. These rates were adjusted with a literature-based factor to reflect a 40% increased risk for bladder cancer in a diabetic population. A standardized incidence ratio was calculated to compare observed case numbers in the dapagliflozin arms to expected numbers in an age-matched diabetic background population.

In the clinical trials of dapagliflozin, no cases of bladder cancer were observed in female patients. Nine cases occurred during a total follow-up of 2,237.1 subject-years in males in the dapagliflozin arms, amounting to a rate of 402 (95% CI, 184 – 764) per 100,000 subject-years. This compared to 1 case during 989.8 subject-years in male controls, or 101 (95% CI, 1.3 – 562) new cases per 100,000 subject years. The two-sided p-value comparing the incidence of bladder cancer between active treatment and controls was 0.28 for males. Based on SEER data, only two cases would be expected in the male dapagliflozin population, at a rate of 91.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 4.39 (95% CI, 2.01 – 8.33), $p < 0.001$. Consistent with actual occurrence, one case would be expected among the male controls.

To summarize, the clinical trials were not powered to statistically distinguish between 9 cases of bladder cancer in the active treatment arms compared to 1 case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Limitations suggest that comparisons between clinical trial data and a reference population should be interpreted with caution.

1 BACKGROUND

In the phase 2b and phase 3 clinical trial program of dapagliflozin (NDA 202293), the sponsor (Bristol-Myers Squibb and AstraZeneca) reported 10 subjects with a diagnosis of bladder cancer; all of these subjects were males. Nine of these cases occurred in the active treatment arms and one in a placebo arm. To provide context for these observations, the Division of Metabolism and Endocrinology Products (DMEP) requested a review of the background rate of bladder cancer in the diabetic population. DMEP further requested information on the background rate of breast cancer to address similar concerns. Information on breast cancer is the subject of a parallel review by Dr. Jing (Julia) Ju, Division of Epidemiology I, Office of Pharmacovigilance and Epidemiology.

2 METHODS

For this review, age- and sex-specific incidence rates of bladder cancer in the US general population were extracted from the Surveillance Epidemiology and End Results (SEER) database

of the National Cancer Institute. This rate was adjusted with a literature-based factor to reflect the increased risk for bladder cancer in a diabetic population. For the male participants in the dapagliflozin clinical trial program, observed case counts were compared to expected case counts in an age-matched diabetic background population.

3 RESULTS

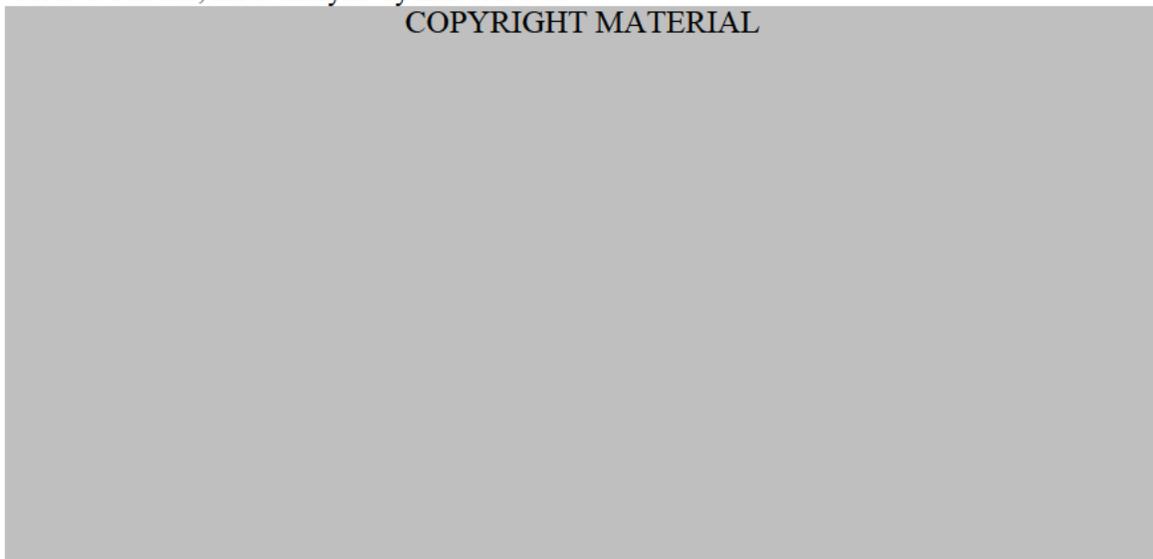
3.1 LITERATURE REVIEW

The National Cancer Institute estimates that 52,760 men and 17,770 women developed urinary bladder cancer in 2010, and 14,680 men and women died from it (1). The median age at diagnosis was 73 and the median age at death from bladder cancer was 78.

A meta-analysis, published in 2006, combined 16 observational studies to obtain a summary estimate of bladder cancer risk associated with diabetes mellitus (2). Separate estimates were provided for studies based on whether their estimates were adjusted for a history of smoking (Table 1). Smoking is a strong risk factor for bladder cancer, responsible for up to 25% of incident cases (3). Because smoking is also more prevalent in subjects with diabetes mellitus, it meets the definition of a confounder, and the extent of confounding introduced by smoking is not negligible. For this reason, this review focused on studies that adjusted for smoking and were included in the meta-analysis by Larsson et al., as well as studies published since the meta-analysis, if smoking was included in the analysis. Eight studies from the meta-analysis (1, 3-9) and five studies published since then (10-14) were included in this review.

Table 1. Results, meta-analysis by Larsson et al.

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Source: Larsson et al.(2); reference numbers do not apply to this document

3.1.1 Studies included in meta-analysis

Figure 1 shows effect estimates from the studies that adjusted for smoking (marked with *). These estimates range from a relative risk of 1.0 (95% CI, 0.60 – 1.70) in a study by Rousseau et al.(8) to 2.69 (95% CI, 1.01 – 7.19) in a study conducted by Ng et al.(9). The summary estimate for studies that adjusted for smoking was a relative risk of 1.48 (95% CI, 1.25 – 1.77) for bladder cancer among diabetic patients, compared to non-diabetics. The eight

included studies differ in their outcome definition: one study (4) used *cancer mortality* as primary outcome and did not include *carcinoma in situ* cases. All other studies investigated *new diagnoses of cancer*; some of them explicitly included *carcinoma in situ* cases (3, 5, 7), while the case definition for the remaining studies is unclear in this regard.

Figure 1. Meta-analysis by Larsson et al.

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Source: Larsson et al.(2); reference numbers do not apply to this document

* Studies that included adjustment for smoking and were selected for this review

3.1.2 Studies published after publication of the meta-analysis

Five studies on the risk of bladder cancer associated with diabetes mellitus were published since the meta-analysis (10-14). All of these studies included adjustment for the effects of smoking. In a cohort study in Swedish men, Larsson et al.(10) found no significant increase in the risk for bladder cancer (excluding *carcinoma in situ*) associated with diabetes (rate ratio, 1.16 [0.81 – 1.64]), but the risk increased when only high-grade (grades II or III) cancers were analyzed (rate ratio, 1.48 [0.99 – 2.21]). In a prospective cohort study in European men and women (12), investigators analyzed data based on blood glucose levels and found a higher risk increase for women (hazard ratio, 1.45 [1.05 – 2.01]) than for men (hazard ratio, 1.17 [1.00 – 1.37]) per 1mmol/l increment in blood glucose level. A large retrospective cohort study in Taiwanese men and women older than 40 years at baseline (13) found a hazard ratio associated with diabetes of 1.39 (95% CI, 1.12 – 1.72) in both sexes combined. This study did not include *carcinoma in situ* cases. A recent 10-year prospective cohort study conducted in Hawaii and Los Angeles (14) found a small, nonsignificant increase in risk for urothelial cancer in men of 1.18 (95% CI, 0.96 – 1.47) and a significant increase of 1.48 (95% CI, 1.02 – 2.14) in women; however, the interaction was not significant (p=0.19). Of note, this study found essentially the same effect of diabetes on *carcinoma in situ* or localized cancers (relative risk, 1.23 [0.99 – 1.51]) as on regional or distant cancers (relative risk, 1.25 [0.78 – 2.00]). Finally, MacKenzie et al. (11) conducted a case-control study in New Hampshire and found a risk increase for bladder cancer associated with diabetes (odds ratio, 2.2 [1.3 – 3.8]), not appreciably different based on age or sex. This study found a stronger association for noninvasive cancer (odds ratio, 2.8 [1.6 – 4.9]) than for invasive cancer (odds ratio, 1.5 [0.7 – 3.2]) but it is acknowledged that this difference could be due to chance.

3.1.3 Diabetes and bladder cancer by sex

Unfortunately, the meta-analysis did not provide sex-specific estimates on the risk of bladder cancer associated with diabetes mellitus.

Only one study was conducted solely in women (3) and found a significant increase in the risk for bladder cancer associated with diabetes (relative risk, 2.46 [1.32 – 4.59]).

Two studies were conducted solely in men and found either no increase in risk (odds ratio, 1.0 [0.6 – 1.7]) (8) or a small, non-significant overall increase associated with diabetes (rate ratio, 1.16 [0.81 – 1.64]), but the risk increased when only high-grade (grades II or III) cancers were analyzed (rate ratio, 1.48 [0.99 – 2.21]).

Several studies included both sexes and provided sex-specific risk estimates for bladder cancer associated with diabetes. Coughlin et al.(4) found an increased risk for fatal bladder cancer in men (relative risk, 1.43 [1.14 – 1.80]) and a non-significant increase in fatal bladder cancer in women (relative risk, 1.30 [0.85 – 2.00]). A study in Koreans (15) reported an increase for men (hazard ratio, 1.32 [1.10 – 2.67]), but provided no estimate for women. In contrast, a European study (12) found a higher risk of bladder cancer per 1mmol/l increment in blood glucose level in women (hazard ratio, 1.45 [1.05 – 2.01]) than in men (hazard ratio, 1.17 [1.00 – 1.37]). Similarly, Woolcott et al. (14) found a higher increase in risk for urothelial cancer in women (rate ratio, 1.48 [95% CI, 1.02 – 2.14]) than in men (relative risk, 1.18 [95%CI, 0.96 – 1.47]). The remaining studies did not provide separate risk estimates by sex.

Taken together, these studies did not provide conclusive evidence of a differential risk increase for bladder cancer associated with diabetes mellitus in women versus men.

3.1.4 Summary of Literature Review

Although not all studies published after the meta-analysis found statistically significant increases in the risk for bladder cancer associated with diabetes mellitus, almost all point estimates suggested a possible increase. The order of magnitude of these estimates is comparable with what the meta-analysis found in studies that adjusted for smoking. Therefore, this review used the summary estimate from the 8 studies that adjusted for smoking found in the meta-analysis (hazard ratio, 1.48 [1.25 – 1.77]) to adjust SEER data to provide a background incidence rate for bladder cancer in the diabetic population in the U.S.

3.2 SEER DATA EXTRACTION

The hazard ratio for bladder cancer associated with diabetes was derived from studies that compared diabetic populations to non-diabetics. However, SEER data provide estimates for the US general population, which includes diabetic subjects. Thus, multiplying the SEER estimates with the hazard ratio of 1.48 would result in an overestimated incidence for a diabetic population. According to the American Diabetes Association, 11.3% of all Americans older than 20 years have diabetes (16). For this review, a downward-adjusted hazard ratio of 1.40 was calculated and applied to a population with an 11.3% prevalence of diabetes to provide the same incidence rate for a pure diabetic population as the hazard ratio of 1.48 when applied to a pure non-diabetic population.

Tables 2 and 3 provide age- and sex-specific incidence rates for bladder cancer in the US general population and projected incidence rates for the diabetic population. Both age and sex are strongly associated with the risk for bladder cancer. Table 3 provides different age categories and, in addition, staging information. These data suggest little difference in cancer stages based

on age or sex. SEER data include *carcinoma in situ* cases and so did the sponsor's definition, as communicated to FDA on 5/27/2011 in a response to a related inquiry from 5/26/2011.

Table 2. Incidence rates for bladder cancer based on SEER data, 2000 - 2008

Age at diagnosis	Males		Females	
	Incidence, general population*	Projected incidence, diabetic population*	Incidence, general population*	Projected incidence, diabetic population*
15-19	0.1	0.2	--	--
20-24	0.3	0.4	0.2	0.2
25-29	0.5	0.7	0.3	0.4
30-34	1.1	1.5	0.4	0.6
35-39	2.3	3.2	0.9	1.3
40-44	5.0	7.0	1.8	2.6
45-49	11.2	15.6	3.7	5.1
50-54	22.7	31.8	7.2	10.0
55-59	45.6	63.8	12.7	17.8
60-64	79.8	111.8	21.8	30.5
65-69	130.8	183.1	34.4	48.1
70-74	196.6	275.3	46.0	64.4
75-79	266.0	372.5	60.4	84.6
80-84	325.4	455.5	73.6	103.0
85+	362.1	506.9	79.1	110.7

*per 100,000 person-years

Table 3. Incidence rates for bladder cancer based on SEER data, 2000 - 2008

	Age at diagnosis	Incidence, general population*	Projected incidence, diabetic population*	Stages [%]			
				Localized	Regional	Distant	Unstaged
Males	20-49	3.1	4.3	69.4	15.9	8.8	5.9
	50-64	39.6	55.5	70.6	16.2	7.7	5.5
	65-74	147.8	206.9	73.2	15.2	6.5	5.1
	75+	297.4	416.3	74.0	12.4	6.0	7.6
Females	20-49	1.1	1.5	59.1	20.2	14.2	6.5
	50-64	11.8	16.5	65.5	18.4	10.3	5.8
	65-74	36.5	51.1	67.3	17.4	10.0	5.4
	75+	66.4	92.9	69.1	12.5	8.7	9.7

*per 100,000 person-years

3.3 COMPARISON WITH CLINICAL TRIAL DATA

At the time of writing this review, 10 subjects were reported as having been diagnosed with bladder cancer in the phase 2b and phase 3 clinical trials on dapagliflozin. Nine of these cases occurred in the active treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76. Diagnoses were made between study day 43 and 727. Total follow-up of male patients randomized to dapagliflozin was 2,237.1 subject-years (Table 4). With nine cases of bladder cancer occurring during this time, this rate amounts to 402 (95% CI, 184 – 764) new cases per 100,000 subject-years. This compares to 1 case during 989.8 subject-years in controls, or 101 (95% CI, 1.3 – 562) new cases per 100,000 subject-years. The two-sided p-value comparing the incidence of bladder cancer between active treatment and controls was 0.28 (Fisher’s exact). The rate ratio between active treatment and control was 3.98 [95% CI, 0.51 – 31.4]. These estimates are pooled summary estimates and do not take heterogeneity between clinical trials into account, including potential imbalances in active treatment versus control ratios that may introduce confounding.

Based on SEER data, only two cases (2.05) would be expected in the male dapagliflozin population (Table 4) at a rate of 91.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 4.39 (95% CI, 2.01 – 8.33), $p < 0.001$. Consistent with actual occurrence, one case would be expected among the male controls.

In comparison, 0.5 cases would be expected in the female subjects exposed to dapagliflozin, at a rate of 23.5 per 100,000 subject-years. In female controls, 0.22 cases would be expected. No cases of bladder cancer were observed either in the dapagliflozin or control arms.

Table 4. Expected cases of bladder cancer in the male clinical trial sample

Age at diagnosis	Males			Expected bladder cancer cases in dapagliflozin patients
	Observed cases, dapagliflozin	Dapagliflozin, person-time, males	Projected incidence, diabetic population*	
<25	0	1.4	0.4	0.0000
25-29	0	15.6	0.7	0.0001
30-34	0	43.7	1.5	0.0007
35-39	0	81.6	3.2	0.0026
40-44	0	160.7	7.0	0.0113
45-49	1	274	15.6	0.0428
50-54	0	332.6	31.8	0.1058
55-59	1	445.7	63.8	0.2844
60-64	2	395.6	111.8	0.4421
65-69	3	277.2	183.1	0.5077
70-74	2	146.1	275.3	0.4022
75-79	0	49.8	372.5	0.1855
80-84	0	12.7	455.5	0.0578
85+	0	0.4	506.9	0.0020
sum	9	2237.1	--	2.05

4 DISCUSSION

This review provides background incidence rates for bladder cancer in the US general population and projected incidence rates for the diabetic population. Several mechanisms have been suggested to explain the increased risk in diabetics. Insulin has a mitogenic effect and increased insulin levels in the blood could stimulate tumor growth by increasing bioactive insulin-like growth factor-1 (17). Alternatively, diabetes is associated with changes in urine composition and bladder function as well as an increased risk for urinary tract infections, which, in turn, are linked with increased risk for bladder cancer (6).

Findings of this review should be viewed in the light of several limitations. Cancer rates in SEER reflect the US general population, while most of the clinical trial subjects were enrolled outside of the US. This could impact comparability, since, for instance, Asian populations are at lower risk for bladder cancer. A Korean study found only 22.3 cases per 100,000 subject-years in diabetic men (15) compared to 53.9/100,000 subject-years in diabetic women in Iowa (3) and 142.8/100,000 subject-years in diabetic men in Sweden, although the latter did not include *carcinoma in situ* cases (10). Also, clinical trial populations are often highly pre-screened for certain co-morbidities, which may result in an underestimated cancer incidence. Nevertheless, both limitations would result in a lower case count and therefore, the risk of bladder cancer associated with exposure to dapagliflozin would be underestimated. On the other hand, increased surveillance in a clinical trial setting, together with urinary symptoms associated with dapagliflozin could increase case detection of bladder cancer and lead to higher estimates compared to the background population. Lastly, it should be considered that the literature-based factor to adjust SEER estimates for a diabetic population is subject to uncertainty.

To summarize, the clinical trials were not powered to statistically distinguish between 9 cases of bladder cancer in the active treatment arms compared to 1 case in the control arms. However, event rates for males observed in the active treatment arms significantly exceeded the rates expected in an age-matched reference diabetic population. Limitations suggest that comparisons between clinical trial data and a reference population should be carefully interpreted.

Christian Hampp, PhD

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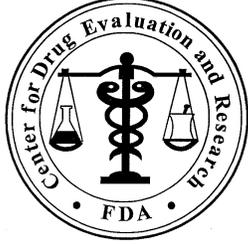
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 2, 2011

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Subject: Review of epidemiological study entitled "Incidence of urinary tract infection and genital infection among patients with type 2 diabetes in UK General Practice Research Database."

Drug Name(s): Dapagliflozin

Submission Number:

Application Type/Number: NDA 202293

Applicant/sponsor: Bristol Myers Squibb

OSE RCM #: 2011-340

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EXECUTIVE SUMMARY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), an observational study report for study MB102049 (dated 09-Nov-2010) in support of the New Drug Application (NDA) of dapagliflozin titled “Incidence of urinary tract infection and genital infection among patients with type 2 diabetes in the UK General Practice Research Database” (GPRD) was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE).

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose co-transporter, the major transporter responsible for renal glucose reabsorption. This new molecular entity (NME) is currently undergoing NDA review as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin lowers both fasting and postprandial plasma glucose by inhibiting the renal reabsorption of glucose and by promoting its urinary excretion. The dapagliflozin sponsors are Bristol-Myers Squibb and AstraZeneca.

Genital infections and urinary tract infections (UTIs) are considered adverse events of special interest given that dapagliflozin causes glucosuria. In clinical trials of dapagliflozin, the main analysis of safety showed that genital infections and UTIs were more common in the dapagliflozin 5 and 10 mg groups compared with the 2.5 mg and placebo groups. The primary objective of this observational study was to quantify the overall incidence rates of UTIs, vaginitis, and balanitis among type 2 diabetes patients in the GPRD.

The overall incidence of UTIs was 46.9 per 1,000 person-years (95% confidence interval [CI], 45.8-48.1) among diabetes patients and 29.9 per 1,000 person-years (95% CI, 28.9-30.8) among non-diabetes patients. The incidence of vaginitis was 21.0 per 1,000 person-years (95% CI, 19.8-22.1) among diabetes patients versus 10.3 per 1,000 person-years (95% CI, 9.5-11.1) among non-diabetes patients. The incidence of balanitis was 8.4 per 1,000 person-years (95% CI, 7.8-9.1) among diabetes patients versus 2.5 per 1,000 person-years (95% CI, 2.2-2.9) among non-diabetes patients. Compared to non-diabetes patients, the relative risk was 1.53 (95% CI, 1.46-1.59), 2.04 (95% CI, 1.8-2.3),

and 3.4 (95% CI, 2.8-4.0) among type 2 diabetes patients for UTIs, vaginitis, and balanitis, respectively.

This reviewer acknowledges that this is a well-conducted study and tends to agree with the study's conclusion that patients with type 2 diabetes are at an increased risk of being diagnosed with infections of the urinary tract and genital tract compared to patients without diabetes. The study investigators should have adjusted for body mass index (BMI), medications taken at the time of infections or censoring date, immune system disorders, and other relevant comorbidities in the multivariate analyses for the relative risk of UTIs and genital infections. It is unclear how this may have affected the conclusion although adjustment for additional covariates potentially could alter the risk estimates and conclusion. Nevertheless, accepting the conclusion that diabetes have higher frequencies of infections of the urinary tract and genital tract would not explain the higher rates of these infections in diabetic patients randomized to 5 and 10 mg of dapagliflozin treatment arms compared to 2.5 mg dapagliflozin arm and the placebo arm in clinical trials. A direct comparison should not be made between the estimated background incidence rates in this GPRD study and the observed incidence rates of UTIs and genital infections in the dapagliflozin clinical trials because patients enrolled in the dapagliflozin clinical trials who met the inclusion and exclusion criteria are different from the study population in this GPRD study.

1 BACKGROUND/HISTORY

Per a request from the Division of Metabolism and Endocrinology Products (DMEP), an observational study report for study MB102049 (dated 09-Nov-2010) titled "Incidence of urinary tract infection and genital infection among patients with type 2 diabetes in the UK General Practice Research Database" was reviewed by the Division of Epidemiology I (DEPI I) in the Office of Surveillance and Epidemiology (OSE).

Dapagliflozin is a highly potent, selective, and reversible inhibitor of the human renal sodium glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. This new molecular entity (NME) is currently undergoing NDA review as an adjunct to diet and exercise to improve glycemic control in adults with

type 2 diabetes mellitus. Dapagliflozin lowers both fasting and postprandial plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion.

Genital infections and UTIs are considered adverse events of special interest given that dapagliflozin causes glucosuria. In clinical trials of dapagliflozin, the main analysis of safety showed that genital infections and UTIs were more common in the dapagliflozin 5 and 10 mg groups compared with the 2.5 mg and placebo groups. Events suggestive of UTIs in short-term plus long-term treatment trials were as follows: 6.6%, 7.2%, 10.4%, and 10.0% in study arms of placebo, dapagliflozin 2.5 mg, 5 mg, and 10 mg, respectively. Events suggestive of genital infections in short-term plus long-term treatment trials were as follows: 2.9%, 8.5%, 10.0%, and 10.8% in study arms of placebo, dapagliflozin 2.5 mg, 5 mg, and 10 mg, respectively. The sponsor conducted this observational study on the incidence of UTIs and genital infections among patients with type 2 diabetes in the UK's General Practice Research Database (GPRD) to provide the epidemiology context for the disease outcomes observed in the dapagliflozin clinical trials.

The primary objective of this observational study was to quantify the overall incidence rates of UTIs, vaginitis, and balanitis among type 2 diabetes patients. Two main research questions addressed by this study were: 1) what are the background rates of UTIs, vaginitis, and balanitis among type 2 diabetes and non-diabetes patients? and 2) what are the incidence rates of these events when stratified by prognostic factors including gender and age?

2 REVIEW MATERIALS

The observational study report for study MB102049 (dated 09-Nov-2010) titled "Incidence of urinary tract infection and genital infection among patients with type 2 diabetes in the UK General Practice Research Database" was reviewed.

3 RESULTS OF REVIEW

3.1 STUDY SYNOPSIS

A retrospective cohort study was conducted by Bristol-Myers Squibb and AstraZeneca to quantify the overall incidence rates of UTI, vaginitis, and balanitis among type 2 diabetes patients in the GPRD.

All patients, aged 18 years or older on index date (the date of the first type 2 diabetes diagnosis or the date of the first record of an oral antidiabetes drug (OAD) in the database) with a diagnosis of type 2 diabetes from January 1, 1990 through December 31, 2007 were identified. A cohort of non-diabetes patients were frequency matched to the diabetes cohort on age, gender, and year of index date. All patients were followed for the incidence of the following outcomes: UTIs, vaginitis, and balanitis for the period of one year from their index date. Medical and prescription records were used to identify each of the study outcomes.

A total of 135,920 type 2 diabetes patients and a 1:1 matched sample of non-diabetic patients were included in the analysis for UTI incidence; 62,537 female type 2 diabetes patients and a 1:1 matched sample of non-diabetic patients were included in the analysis for vaginitis incidence; and 73,383 male type 2 diabetes patients and a 1:1 matched sample of non-diabetic patients were included in the analysis for balanitis incidence.

Separate analyses were conducted for each of the infection-related outcomes. Descriptive statistics were generated for demographic characteristics and relevant baseline co-morbidities. Incidence rates were stratified according to age, gender, diabetes treatment at the time of the initial infection event, and history of infection prior to the index date. Relative risk (RR) of each infection was estimated using multivariate analyses using the non-diabetes cohort as the reference group. Age and gender-adjusted RRs were calculated.

The overall incidence of UTIs was 46.9 per 1,000 person-years (95% confidence interval [CI], 45.8-48.1) among diabetes patients and 29.9 per 1,000 person-years (95% CI, 28.9-30.8) among non-diabetes patients. The incidence of vaginitis was 21.0 per 1,000 person-years (95% CI, 19.8-22.1) among diabetes patients versus 10.3 per 1,000 person-years (95% CI, 9.5-11.1) among non-diabetes patients. The incidence of balanitis was 8.4 per 1,000 person-years (95% CI, 7.8-9.1) among diabetes patients versus 2.5 per 1,000 person-years (95% CI, 2.2-2.9) among non-diabetes patients.

Compared to non-diabetes patients, the RR was 1.53 (95% CI, 1.46-1.59), 2.04 (95% CI, 1.8-2.3), and 3.4 (95% CI, 2.8-4.0) among type 2 diabetes patients for UTIs, vaginitis, and balanitis, respectively.

The study concluded that the risks of developing UTIs and infections of the genital tract are greater for patients with type 2 diabetes compared to patients without diabetes.

3.2 SPECIFIC STUDY ELEMENTS & DEPI COMMENTS

3.2.1 Study Objectives

Study Objectives:

The primary objective of the study was to quantify the overall incidence rates of UTIs, vaginitis, and balanitis among type 2 diabetes patients. The secondary objectives were: 1) to quantify the background rate of UTIs, vaginitis, and balanitis among type 2 diabetes subjects by potential prognostic factors including age, gender, HbA1c, and diabetes treatment at the time of infection; 2) to quantify the background rate of UTIs, vaginitis, and balanitis among a cohort of non-diabetes subjects; and 3) to quantify the relative risk of UTIs, vaginitis, and balanitis between patients with diabetes and those without diabetes.

Reviewer Comments:

This reviewer agrees that the proposed study objectives are appropriate.

3.2.2 Study Design

Proposed Study Design:

This study was a population-based retrospective cohort study.

Reviewer Comments:

This reviewer agrees that a retrospective cohort study is appropriate.

3.2.3 Data Source

Description of Data Source:

This study used the General Practice Research Database (GPRD), a large computerized database of anonymized longitudinal medical records from primary care. Information recorded in the GPRD includes drug prescriptions, medical diagnoses, and patient demographic information.

Reviewer Comments:

This reviewer agrees that the use of GPRD data in this study is appropriate.

3.2.4 Study Time Period

Study Time Period:

This study identified diabetes patients in GPRD between January 1, 1990 and December 31, 2007. Person-time at risk was accrued from the index date until one of the following: diagnosis of study outcomes, transferring out of the GPRD practice, death, or the end of the study follow-up period on April 30, 2008.

Reviewer Comments:

This reviewer agrees that the study time period is appropriate.

3.2.5 Study Population

Study Population:

Patients eligible to enroll in this study were at least 18 years of age on the study index date (the date of the first type 2 diabetes diagnosis or the date of the first record of an oral antidiabetes drug (OAD) in the database), and had a minimum of 6 months enrollment with a general practitioner who contributed data to the GPRD database before the index date. Patients were excluded if they had less than 3 months of data following the index date, diagnosis codes indicative of type 1 diabetes, received exclusive insulin therapy during the first 3 months post diagnosis, or were less than 25 years of age whose initial diabetes treatment was recorded as insulin.

Patients were classified as type 2 diabetes patients if they met one of the following criteria: 1) a diagnosis of type 2 diabetes; or 2) two continuous prescriptions for the treatment of type 2 diabetes. A random sample of patients without diabetes was matched to patients with diabetes on age, gender, and index year.

Reviewer Comments:

This reviewer agrees that the study population and the inclusion and exclusion criteria are appropriate.

3.2.6 Disease Outcome of Interest

Disease Outcome of Interest:

The outcome measures are incident cases of UTIs, vaginitis, and balanitis within a one year follow-up period. Potential outcomes were identified in GPRD using Read codes and standard treatment regimens (antibiotic therapy) for these outcome conditions.

Reviewer Comments:

This reviewer agrees that the outcome measures and the outcome identification strategies are appropriate.

3.2.7 Analyses

Analyses:

Incidence rates were estimated by dividing the number of new events by total person-time at risk. Person-time calculation for patients ended at first occurrence of the following: 1) first infection event; 2) transferring out of the GP practice; 3) last data collection for practice; 4) death; or 5) end of one-year follow-up. Incidence rates were stratified by age categories (18-39, 40-49, 50-59, 60-69, 70+ years), gender, and history of infection within 6 months prior to the index date for both diabetes and non-diabetes patients. For the diabetes cohort, incidence rates were further stratified by history of diabetes and diabetes treatment regimen (no treatment, oral antidiabetes drug, insulin only, combination oral antidiabetes drug and insulin) recorded within 30 days of an infection event or censored event.

A Cox-proportional hazard regression model was used to estimate the hazard ratios of study outcome events for diabetes vs. non-diabetes patients. Covariates adjusted for in the multivariate analysis included age, gender, index year, and history of infection. Additionally, risk estimates of infection were calculated for each age category, controlling for index year and history of infection for patients with and without diabetes, respectively.

Reviewer Comments:

This reviewer believes that other important covariates besides age, gender, index year, and history of infection should have been included in the multivariate analysis. Such covariates include BMI, medications taken at the time of infections or censoring date, immune system disorders¹, and other relevant comorbidities. It is unclear how this may have affected the conclusion although adjustment for additional covariates potentially could alter the risk estimates and conclusion. Nevertheless, accepting the conclusion that diabetes have higher frequencies of infections of the urinary tract and genital tract would not explain the higher rates of these infections in diabetic patients

randomized to 5 and 10 mg of dapagliflozin treatment arms compared to 2.5 mg dapagliflozin arm and the placebo arm in clinical trials.

3.2.8 Study Results

Study Results:

The overall study population included 135,920 type 2 diabetes patients and a 1:1 matched sample of patients without diabetes. The genital infection studies comprised 62,537 female diabetes patients, 62,700 matched female controls, 73,383 male diabetes patients, and 73,220 matched male controls.

The results of the UTI analyses showed following incidence rates:

- 29.9 per 1,000 person-years (95% CI, 28.9-30.8) among non-diabetes patients;
- 46.9 per 1,000 person-years (95% CI, 45.8-48.1) among all diabetes patients (adjusted RR=1.53, 95% CI 1.46-1.59);
- 45.5 per 1,000 person-years (95% CI, 44.3-46.8) among patients with a new diagnosis of diabetes (adjusted RR=1.46, 95% CI 1.40-1.53);
- 58.8 per 1,000 person-years (95% CI, 54.7-62.8) among patients with a previous diagnosis of diabetes (adjusted RR=2.08, 95% CI 1.93-2.24);
- 72.8 per 1,000 person-years (95% CI, 70.6-75.0) among female diabetes patients vs. 45.7 per 1,000 person-years (95% CI, 44.0-47.5) among female non-diabetes patients (adjusted RR=1.53, 95% CI 1.45-1.60);
- 25.5 per 1,000 person-years (95% CI, 24.3-26.7) among male diabetes patients vs. 16.5 per 1,000 person-years (95% CI, 15.5-17.5) among male non-diabetes patients (adjusted RR=1.49, 95% CI 1.38-1.60);
- 49.6 per 1,000 person-years (95% CI, 47.8-51.4) for diabetes patients managed with oral antidiabetes drugs alone;
- 66.8 per 1,000 person-years (95% CI, 44.3-97.1) for diabetes patients treated with regimens including insulin.

The results of the genital infection analyses showed the following incidence rates of vaginitis and balanitis:

- 21.0 (95% CI, 19.8-22.1) among female diabetes patients vs. 10.3 (95% CI, 9.5-11.1) per 1,000 person-years among female non-diabetes patients (adjusted RR=1.81, 95% CI 1.64-2.00);
- 8.4 (95% CI, 7.8-9.4) among male diabetes patients vs. 2.5 (95% CI, 2.1-2.9) per 1,000 person-years among male non-diabetes patients (adjusted RR=2.85, 95% CI 2.39-3.39).

The study concluded that the risks of developing UTIs and infections of the genital tract are greater for patients with type 2 diabetes compared to patients without diabetes across all age groups. Infection incidence increased with the complexity of diabetes treatment with the highest rates occurring for those patients treated with combination of insulin and oral diabetes drugs at the time of infection or censoring date.

Reviewer Comments:

The higher incidence rates of UTIs and genital infections among diabetes patients may be partially attributable to detection bias because of increased physician contact for diabetes patients compared to non-diabetes patients. However, detection bias seems unlikely for severe symptomatic urinary and genital infections which usually require physician consultation. Detection bias may exist for mild infections without symptoms or those can be treated with over-the-counter products. Another potential ascertainment bias may contribute to the higher incidence rates of UTIs and genital infections among diabetes patients because patients are more likely to be identified to have diabetes when they come to be treated for their infections.

Another limitation would be that the incidence rates of UTIs and genital infections may be underestimated for both diabetes and non-diabetes patients. It is unknown whether the magnitudes of potential underestimation differ between the diabetes and non-diabetes cohorts. One source of the underestimation is that the cases identified from the GPRD data represents patients who have sought physician care for an infection and this may include more severe symptomatic cases but not all cases. It is possible that infections encountered in a hospital setting or treated at a specialist clinic may not be captured in the

primary care records. Another source of underestimation is that some vaginitis and balanitis may be self-treated with over-the-counter products, therefore they are not captured in the GPRD data.

Lastly, potential misclassification bias could underestimate the difference in incidence rates of UTI and genital infections between diabetes and non-diabetes cohorts. Some type 2 diabetes patients may be misclassified as not having the disease if they did not have the relevant diagnosis codes or were not taking any antidiabetes medication during the study time period.

4 SUMMARY AND RECOMMENDATIONS

In general, this is a well-conducted study. This reviewer tends to agree with the study's conclusion that patients with type 2 diabetes are at an increased risk of being diagnosed with infections of the urinary tract and genital tract compared to patients without diabetes.

The study investigators should have adjusted for BMI, medications taken at the time of infections or censoring date, immune system disorders, and other relevant comorbidities in the multivariate analyses for the relative risk of UTIs and genital infections. It is unclear how this may have affected the conclusion although adjustment for additional covariates potentially could alter the risk estimates and conclusion. Nevertheless, accepting the conclusion that diabetes have higher frequencies of infections of the urinary tract and genital tract would not explain the higher rates of these infections in diabetic patients randomized to 5 and 10 mg of dapagliflozin treatment arms compared to 2.5 mg dapagliflozin arm and the placebo arm in clinical trials.

A direct comparison should not be made between the estimated background incidence rates in this GPRD study and the observed incidence rates of UTIs and genital infections in the dapagliflozin clinical trials. With the inclusion and exclusion criteria, patients enrolled in the dapagliflozin clinical trials are different from the study population in this GPRD study. In order to assess the risk of UTIs and genital infections associated with dapagliflozin treatment, incidence rates in the dapagliflozin treatment group should be

compared to the rates in the placebo group or other antidiabetic treatment group in clinical trials.

5 REFERENCES

¹ Hammar N, Farahmand B, Gran M, et al. Incidence of urinary tract infection in patients with type 2 diabetes. Experience from adverse event reporting in clinical trials. *Pharmacoepidemiology and Drug Safety*. 2010; 19: 1287-92.

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

/s/

JING JU
05/13/2011

SOLOMON IYASU
05/13/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202293 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: pending Established/Proper Name: Dapagliflozin Dosage Form: tablet Strengths: 5mg, 10mg		
Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable):		
Date of Application: December 27, 2010 Date of Receipt: December 28, 2010 Date clock started after UN:		
PDUFA Goal Date: October 28, 2011	Action Goal Date (if different):	
Filing Date: Feb. 26, 2011	Date of Filing Meeting: Feb. 14, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Type 2 Diabetes Mellitus		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 68652				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Paid \$1542000 on 12.24.2010

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only) N/A</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1440 1349 1577"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<p>X</p>																		

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				N/A
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	N/A			
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			See original submission and submitted 1/5/11 amendment
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			Form 3454 and 3455 and attachment included. Module 1.3.4 contains 618 page financial disclosure package
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with	X			

authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	eCTD submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			XX	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			PeRC Meeting scheduled for September 7, 2011

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>		X		Need to provide evidence that studies are being or will be conducted with due diligence and at the earliest time possible
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Proposed tradename BMS previously requested consideration of (b)(4) as the tradename for dapagliflozin (IND #68,652/SN0304). FDA denied this tradename in a letter dated 19-Nov-2010; hence, BMS plan to submit a new proposed tradename in a separate submission to this NDA.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		Risk Management Plan (RMP) was submitted
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) RMP			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Sponsor submitted PI, PPI, and RMP. OSE will review any submissions of MedGuide or REMs during review of this NDA
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				Whether QT-IRT consult required still pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): October 9, 2008 (CMC); September 11, 2007 (Clinical)	x			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 9, 2011	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): Mouse/Rat carcinogenicity letter fax dated December 19, 2006	x			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 14, 2011

BLA/NDA/Supp #: 202293

PROPRIETARY NAME: pending

ESTABLISHED/PROPER NAME: dapagliflozin

DOSAGE FORM/STRENGTH: tablet/ 5mg, 10mg

APPLICANT: Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Type 2 Diabetes Mellitus

BACKGROUND:

Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose is 10 mg taken once daily at anytime of the day regardless of meals. Dosage form and strengths is 10 mg and 5 mg tablets.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Y
	CPMS/TL:	Lina Aljuburi	Y
Cross-Discipline Team Leader (CDTL)	Ilan Irony		
Clinical	Reviewer:	Somya Verma Dunn	Y
	TL:	Ilan Irony	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

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Appears this way on original

Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Jon Norton/ Anita Abraham (CV meta-analysis)	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mukesh Summan	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Suong Tran (filing); Xavier Ysern	Y
	TL:	Ali Al Hakim	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Xavier Ysern	Y
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lissa Owens- carton and container	Y
	TL:	Carlos Mena-Grillasca- TL for carton and container	Y
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey, Melissa Hulett, Suzanne Berkman Robottom; Quocbao Pham (DPV)	Y
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

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Appears this way on original

Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	ONDQA Biopharmacuetics- Minerva Hughes; Quality Microbiology- Stephen Fong		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Curtis Rosebraugh (ODE II Director)	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
a.	Filing Meeting February 14, 2011
b.	Filing Goal Date February 25, 2011
c.	74-day filing issues March 11, 2011
d.	Mid-Cycle Meeting May 24, 2011
e.	Advisory Committee TBD
f.	Wrap-Up Meeting TBD
g.	PDUFA Action Date October 28, 2011
h.	Complete primary and secondary reviews September 2 and September 9, 2011
i.	Complete CDTL review September 16, 2011
j.	Complete DD review and sign-off October 7, 2011
k.	Complete OD review and sign-off October 28, 2011
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product

	classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

RAYMOND S CHIANG
04/07/2011