

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202293Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202293

SUPPL #

HFD # 510

Trade Name Farxiga

Generic Name dapagliflozin

Applicant Name BMS

Approval Date, If Known January 8, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Abolade (Bola) Adeolu
Title: Regulatory Project Manager
Date: 12/5/2013

Name of Office/Division Director signing form: Curtis Rosebraugh, MD, MPH
Title: Director, ODEII

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ABOLADE ADEOLU
01/07/2014

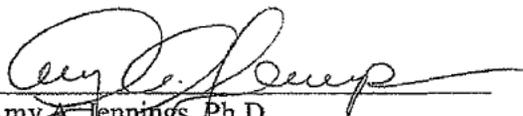
CURTIS J ROSEBRAUGH
01/07/2014

NDA NO. 202-293

DAPAGLIFLOZIN 30 MONTH UPDATE

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



Amy A. Jennings, Ph.D.
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US
Bristol-Myers Squibb Company

28-Jun-2013
28 June-2013

NDA NO. 202-293

NEW DRUG APPLICATION - DAPAGLIFLOZIN

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



Amy A. Jennings
Director, Global Regulatory Strategy
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
860-677-3821

19-NOV-2010
Certification Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202293	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Farxiga Established/Proper Name: dapagliflozin Dosage Form: tablet		Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable):
RPM: Abolade Adeolu		Division: Division of Metabolism and Endocrinology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 11, 2014</u> 	X AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	CR on 1/17/2012	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP – 1/8/2014; CR – 1/17/2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7/11/2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	7/11/2013
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	12/24/2013;11/4/2013; 10/16/2013;7/11/2013;
<ul style="list-style-type: none"> Most-recent draft labeling 	11/4/2013
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Letters: 10/7/2013; 4/26/2011 Reviews:10/7/2013; 12/5/2011; 4/26/2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 12/6/2011 <input checked="" type="checkbox"/> DMEPA 11/19/2013; 12/12/2011 <input checked="" type="checkbox"/> DMPP/PLT 12/18/2013; 12/20/2011 <input checked="" type="checkbox"/> OPDP (DDMAC) 12/20/2013 <input checked="" type="checkbox"/> SEALD 1/9/2014 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	4/7/2011
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	9/7/2011 <input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) 	1/8/2014 (2); 12/20/2013; 12/16/2013; 12/6/2013; 11/22/2013; 10/11/2013; 10/9/2013; 10/4/2013; 10/2/2013; 9/12/2013; 7/25/2013; 12/27/2012; 11/28/2012; 11/19/2012; 9/14/2012; 8/27/2012; 8/16/2012; 7/31/2012; 4/27/2012; 3/22/2012; 1/26/2012; 1/4/2012; 12/19/2011; 12/14/2011; 12/9/2011; 12/7/2011(3); 12/2/2011; 11/28/2011; 11/17/2011; 11/9/2011; 11/7/2011; 11/4/2011; 11/3/2011; 10/31/2011; 10/26/2011; 10/18/2011; 9/29/2011; 9/26/2011; 9/7/2011; 9/1/2011; 8/23/2011; 8/19/2011; 8/18/2011; 8/16/2011; 8/15/2011(2); 8/11/2011; 8/6/2011; 8/5/2011; 8/3/2011; 8/1/2011; 7/13/2011; 7/8/2011; 7/7/2011; 6/28/2011; 6/9/2011(3); 6/6/2011; 6/3/2011(2); 5/31/2011; 5/27/2011; 5/26/2011; 5/25/2011; 5/20/2011; 5/18/2011; 5/17/2011; 5/12/2011(2); 5/11/2011; 5/9/2011; 5/6/2011; 5/5/2011; 5/4/2011; 5/3/2011; 4/28/2011; 4/12/2011(2); 4/8/2011; 3/31/2011; 3/30/2011; 3/29/2011(3); 3/23/2011; 3/9/2011; 3/4/2011; 1/21/2011;1/11/2011
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	9/4/2013
<ul style="list-style-type: none"> ❖ Bnggnb g nbbMinutes of Meetings 	
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	4/30/2012
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	11/9/2010
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	9/11/2007
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	FDRR – 8/15/2012; Type C - 4/30/2012; Type C – 12/4/2009
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	12/12/2013; 7/19/2011
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	12/24/2013; 7/22/2011

Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	1/8/2014; 1/17/2012
Division Director Summary Review (<i>indicate date for each review</i>)	1/8/2013; 12/22/2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	12/24/2013;12/6/2011
PMR/PMC Development Templates (<i>indicate total number</i>)	6 PMRs
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	None – see CDRL review
• Clinical review(s) (<i>indicate date for each review</i>)	12/22/2013; 11/21/2011; 9/2/2011; 2/22/2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	p. 25, 9/2/2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	OSE-11/11/2013 DOP1 – 10/21/2013; 10/3/2013 DPV– 10/4/2013; 11/21/2011; 6/21/2011 DRUP Bone safety – 7/18/2011 MHT – 9/25/2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 11/29/2011; 11/23/2011(3); 9/28/2011; 9/9/2011; 9/8/2011; 7/20/2011; 7/12/2011; 7/8/2011; 6/7/2011; 6/7/2011; 5/13/2011;
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested Reviews: 9/2/2011 Letters: 10/27/2011; 9/7/2011 (2); 8/30/2011; 8/25/2011(4)
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/13/2013; 11/21/2011; 9/9/2011

⁶ Filing reviews should be filed with the discipline reviews.

	DB7: 12/16/2013; 11/22/2011; 9/7/2011; 2/16/2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	12/17/2013; 9/1/2011; 3/1/2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	Pending?
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/13/2012
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/31/2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	12/9/2013; 8/31/2011; 2/15/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc 9/15/2011
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 8/4/2011 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	1/7/2014
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/31/2013; 9/19/2013; 10/31/2011; 9/2/2011; 5/27/2011; 4/27/2011; 2/14/2011; 1/31/2011
❖ Microbiology Reviews	<input type="checkbox"/> Not needed 8/31/2011
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>) Biopharmaceutics	9/19/2013
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	page 193, 9/2/2011
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 10/31/2013; 10/25/2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed N/A <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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

/s/

ABOLADE ADEOLU
01/09/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, January 08, 2014 10:05 AM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: FW: dapa label
Attachments: initnda8dapa14-dapag-pro.doc

Importance: High

Dear Amy,

We note your agreement to the labeling, and accept your revisions dated January 8, 2014.

Bola Adeolu
301 796-4264

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Wednesday, January 08, 2014 9:26 AM
To: Adeolu, Abolade
Subject: dapa label

Bola,

Attached is the updated clean label with (b) (4) text removed after (b) (4) per your request.

Can you tell me when you are planning to send the Action letter so I can be sure to be at my computer?

Thanks
Amy

This message (including any attachments) may contain confidential, proprietary, privileged and/or private information. The information is intended to be for the use of the individual or entity designated above. If you are not the intended recipient of this message, please notify the sender immediately, and delete the message and any attachments. Any disclosure, reproduction, distribution or other use of this message or any attachments by an individual or entity other than the intended recipient is prohibited.

43 Page(s) of Labeling has been Withheld in Full as
duplicate copy of approved final product label
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/

ABOLADE ADEOLU
01/08/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 202293
Product Name: Dapagliflozin

PMR/PMC Description: A randomized, multicenter, parallel, single-dose study to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of dapagliflozin in children, 10 to 17 years of age with type 2 diabetes mellitus (T2DM) receiving one of the three dose levels of dapagliflozin over the range of 2.5 to 10 mg. At least 30% of randomized subjects in each dose group will be 10 - 15 years of age.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2012</u>
	Study/Trial Completion:	<u>08/30/2014</u>
	Final Report Submission:	<u>02/28/2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dapagliflozin is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data is available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This is a deferred pediatric study under the Pediatric Research Equity Act (PREA) to assess the pharmacokinetics (PK), pharmacodynamics (PD) and safety of dapagliflozin in pediatric patients age 10 to < 18 years with T2DM.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous post-marketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, multi-center, parallel, single-dose study to explore the PK and PD of dapagliflozin in children, 10 to 17 years of age with T2DM receiving one of the three dose levels of dapagliflozin over the range of 2.5 to ^(b)₍₄₎ mg. This study will include an assessment of PK and PD (including urinary glucose excretion [UGE] and plasma glucose, and assessment of safety, tolerability and tablet formulation acceptability in children. At least 30% of randomized subjects in each dose group will be 10 to 15 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Subpopulation: Pediatric subjects ages 10 to <18 years with T2DM

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

A clinical pharmacology study to explore the PK and PD of dapagliflozin in children, 10 to 17 years of age with T2DM receiving one of the three dose levels of dapagliflozin over the range of 2.5 to ^(b)₍₄₎ mg. This study will include an assessment of PK and PD (including urinary glucose excretion [UGE] and plasma glucose), and assessment of safety, tolerability and tablet formulation acceptability in children. At least 30% of randomized subjects in each dose group will be 10 to 15 years of age.

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 202293
Product Name: Dapagliflozin

PMR/PMC Description: A 26-week randomized, double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of dapagliflozin compared to placebo in pediatric subjects ages 10 to <18 years with T2DM, as add-on to metformin or monotherapy (at least 30% of patients). Subjects may be rescued as needed during the trial. At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of dapagliflozin on mineral and bone metabolism, and the effect of dapagliflozin on growth.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/31/2015</u>
	Study/Trial Completion:	<u>02/28/2020</u>
	Final Report Submission:	<u>08/31/2020</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Dapagliflozin is ready for approval for use in adults; however, pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study required under PREA to assess the efficacy and safety of dapagliflozin compared with placebo when added on to metformin or as monotherapy for the treatment of T2DM in pediatric subjects ages 10 to <18 years. SGLT2 inhibitors alter body weight, renal transport of several minerals (i.e., calcium, magnesium and phosphorus), parathyroid hormone and vitamin D metabolism. There was no fracture imbalances, clinically meaningful changes in bone biomarkers or bone mineral density overall in the completed clinical program. This needs to be assessed in the pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of dapagliflozin for the treatment of pediatric subjects ages 10 and <18 years of age with T2DM, as add-on to metformin or as monotherapy, followed by a 26-week double-blind, placebo- or active-controlled extension period (Week 26 to Week 52). At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10 to 14 years and 15 to <18 years) will be female. Secondary safety endpoints should include the effect of dapagliflozin on mineral and bone metabolism, and the effect of dapagliflozin on growth.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Subpopulation: Pediatric subjects ages 10 to <18 years with T2DM

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? (*difficulties with enrollment and trial duration for pediatric studies in T2DM for all anti-diabetic agents is being discussed further internally*)

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 202293
Product Name: Dapagliflozin

PMR/PMC Description: Evaluation of dapagliflozin in an orthotopic rodent bladder tumor promotion model.

PMR/PMC Schedule Milestones: Final Protocol Submission: 11/30/2014
Study/Trial Completion: 11/30/2015
Final Report Submission: 08/31/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There was a numerical imbalance in the diagnoses of bladder cancer in the clinical program for dapagliflozin: 10 bladder cancer cases among 6045 dapagliflozin-treated patients (0.17%) vs. 1/3512 (0.03%) patients in the comparator arm. The incidence rate ratio (IRR) was 6.11 (95% CI, 0.83 to 272.02). Based on review of these cases, the literature, and pharmacovigilance data from countries where dapagliflozin was approved, it was unclear if this represents a true signal or a chance finding. The current weight of evidence from nonclinical studies indicates that dapagliflozin by itself does not act as a carcinogen. However, evaluation of tumor promotion in 2-yr rodent studies was limited by the lack of background neoplastic and pre-neoplastic bladder lesions. A study in an orthotopic model of bladder tumor promotion in rodents is intended to address this issue and potentially provide additional guidance for appropriate use of dapagliflozin.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The numerical imbalance of diagnoses of bladder cancer in clinical trials might have arisen by chance, but potentially also from tumor promotion secondary to changes in the microenvironment of the bladder *in vivo*. Dapagliflozin is to be evaluated in an orthotopic rodent bladder tumor promotion model that best simulates clinical experience. The required studies should adequately evaluate for bladder tumor promotion *in situ* secondary to changes in the microenvironment of the bladder and renal function in response to dapagliflozin.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Evaluate dapagliflozin in a rodent bladder tumor promotion model that best simulates clinical experience. This should adequately evaluate for bladder tumor promotion *in situ* secondary to changes in the microenvironment of the bladder and renal function in response to dapagliflozin.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

There was one case of hepatitis in the clinical program which met Hy's law criteria, adjudicated as autoimmune hepatitis for which an association to dapagliflozin could not be excluded. No imbalance in increases in minor ALT elevations of clinical consequence due to study drug have been observed. The majority of cases of transaminase and bilirubin elevations had other diagnoses that were more likely than dapagliflozin to have caused the test abnormalities. Enhanced pharmacovigilance is required to assess the potential for hepatotoxicity once the product has been used in a larger patient population.

In rat studies, exposure to dapagliflozin was associated with an increased incidence and/or severity of renal pelvic and tubular dilatations in offspring. These outcomes occurred with drug exposures during periods of animal development that correlate with the second and third trimesters of human pregnancy. Dapagliflozin is not recommended to be used in the second and third trimesters of pregnancy. Enhanced pharmacovigilance is required to generate additional data on the effect of dapagliflozin exposure during pregnancy to assess the potential for dapagliflozin related adverse effect on the fetus and offspring.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the enhanced pharmacovigilance is to gather additional data on known and potential serious risks related to the long-term use of dapagliflozin.

This program will include:

1. Active query of reporters to obtain additional clinical information for reports of hepatic abnormalities and pregnancy.

For reports of serious hepatic abnormalities, the applicant should actively query reporters for liver-related laboratory (including viral serology), imaging and pathology results, duration of dapagliflozin exposure, dose of dapagliflozin, and other risk factors for hepatic abnormalities.

For reports of pregnancy, the applicant should actively query reporters for comorbid conditions, concomitant medication use, other relevant exposures (smoking, alcohol), duration of dapagliflozin exposure, dose of dapagliflozin, action taken with dapagliflozin and the week of gestation at which the action was taken, and the outcome of the pregnancy.

2. In addition to postmarketing reporting requirements as specified in 21 CFR 314.80 and 21 CFR 314.81, FDA requests expedited reporting of all initial and follow-up reports of serious hepatic abnormalities and adverse outcomes of pregnancy

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period. The annual summary and analysis will also include pertinent findings from ongoing or newly analyzed clinical trials and findings from the published medical literature.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Enhanced pharmacovigilance program for reports of serious hepatic abnormalities and pregnancy for a period of 5 years from the date of approval. The enhanced pharmacovigilance will enable collection of data that will be analyzed to better define these risks and includes the following:

- Active query of reporters to obtain additional clinical information related to reports of serious hepatic abnormalities and pregnancy.
- Expedited reporting to FDA of all initial and follow-up reports of serious hepatic abnormalities and adverse pregnancy outcomes.

Interim analyses and summaries of new and cumulative safety information must be submitted annually, followed by the final report at the conclusion of the monitoring period.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Enhanced pharmacovigilance

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Enhanced Pharmacovigilance

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of T2DM should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the 2008 Guidance to Industry, "*Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*". This meta-analysis is intended to demonstrate that dapagliflozin therapy does not result in an unacceptable increase in the risk for MACE (i.e., non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death). The applicant has already provided sufficient evidence that dapagliflozin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded an unacceptable level of cardiovascular risk. In the pre-specified meta-analysis of all phase 2/3 trials, the hazard ratio (HR) for the primary endpoint (CV death, myocardial infarction, stroke and hospitalization for unstable angina) was 0.81 (95% CI of 0.59-1.09). However in 2 placebo-controlled trials (D169C0C00018 and D169C00019) that enrolled patients at higher risk for cardiovascular disease, the HR was 0.98 (95% CI 0.64-1.49). Therefore, consistent with the above guidance, the primary objective of the required post-marketing trial (DECLARE) is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with canagliflozin to that observed with placebo is less than 1.3.

Signals for potential liver toxicity, breast and bladder cancer, bone fractures, nephrotoxicity/acute kidney injury, complicated genital infections that are drug resistant or require hospitalization, urinary tract infections that are drug resistant or require hospitalization/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions, that were noted in the clinical program should also be further assessed in this trial. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for any worsening of renal function.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM at high risk for cardiovascular disease. The primary endpoint will be the time to first occurrence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke.

The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The eGFR should also be monitored over time to assess for any worsening of renal function.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-

X Other

(DECLARE, Study D1693C00001)

A randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with T2DM. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death). Adverse events (AEs) of special interest to include complicated urinary tract and genital infections that require hospitalizations including pyelonephritis, atypical infections or multidrug resistant organisms, acute kidney injury/nephrotoxicity, malignancies (specifically breast and bladder cancer), serious hypovolemic events, hepatotoxicity, bone fractures and serious hypersensitivity reactions. The eGFR should also be monitored over time to assess for any worsening of renal function. The sponsor will submit a protocol amendment for FDA review on January 2014 to include these AEs.

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

X Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

X There is a significant question about the public health risks of an approved drug

X There is not enough existing information to assess these risks

X Information cannot be gained through a different kind of investigation

X The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

X he trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 202293

Product Name: Dapagliflozin

PMR/PMC Description: Adequate follow-up beyond completion of the cardiovascular outcome trial to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	01/31/2015
	Study/Trial Completion:	06/31/2024
	Final Report Submission:	12/31/2024
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During the first review cycle for this NDA (submitted 12/28/10), there was an imbalance for bladder cancer cases. Nine cases/5501 (0.16%) patients in the dapagliflozin treatment arm vs. 1/3184 (0.03%) in the all comparator arm. The incidence rate ratio (IRR) was 5.38 (95% CI, 0.84 to 122.10). With this NDA resubmission an additional case in the dapagliflozin arm was noted, making the IRR 6.11 (95% CI 0.83-272.02). While 6/10 patients had baseline hematuria, 7/10 were over age 65, 9/10 were males, 7/10 were smokers and 5/10 were diagnosed within 6 months of randomization, baseline characteristics between treatment arms were balanced for risk factors. Detection bias due to higher rates of urogenital adverse events (AEs) among dapagliflozin-treated patients was not noted. There is no evidence of tumor initiation/promotion in 2-year rodent studies with dapagliflozin. The Division of Pharmacovigilance I evaluated postmarketing reports in approved countries for dapagliflozin and canagliflozin (to assess a possible class effect), FDA Adverse Events Reporting System (FAERS), Vigibase and the Medical literature. Five bladder cancer cases were noted, all with canagliflozin (all post-approval). Hence, whether this represents a true signal or chance finding is unclear, and it is felt that additional long-term safety data obtained through observational follow-up of patients enrolled in the cardiovascular outcome trial, DECLARE, will best address this question. This could add a substantial amount of patient-years of exposure for follow-up and monitoring, while preserving some benefits of randomization and blinding. The pharmacoepidemiology studies ^{(b) (4)} using databases in the European Union are inadequately powered to address the issue, and there is concern for potential channeling of the drug to patients at low risk for bladder cancer.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Adequate observational follow-up beyond completion of the cardiovascular outcome trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

To best preserve blinding and randomization over the course of the follow-up study:

- a. Participants should only be informed of their treatment assignment if they request this information.
- b. To minimize detection bias and maximize outcome ascertainment, regular screening as done during the randomized controlled trial phase should be continued in the observational follow-up study and all potential cases of bladder cancer should be adjudicated by adjudicators blinded to exposure status. Since subjects would probably use other approved anti-diabetic therapy during observational follow-up, time-dependent multivariate adjustment for concomitant therapy should be considered in a sensitivity analysis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study will be a long-term, observational follow-up extension of the cardiovascular outcomes trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

- X There is not enough existing information to assess these risks
 - X Information cannot be gained through a different kind of investigation
 - X The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - X The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

SUCHITRA M BALAKRISHNAN
01/08/2014

Adeolu, Abolade

From: Jennings, Amy <amy.jennings@bms.com>
Sent: Friday, December 20, 2013 5:22 PM
To: Adeolu, Abolade
Cc: Jennings, Amy
Subject: RE: Dapagliflozin proposed PI and MG
Attachments: Dapa PMR milestone dates -Dec-2013 for FDA.docx

Hi Bola,

Thank you for the label comments. The team will strive to respond by Monday as requested below but it may be more like end of day Monday. Is this ok?

Also, Please find attached the PMRs we captured from the meeting and target milestone dates

Have a nice weekend,
Amy

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Friday, December 20, 2013 12:16 PM
To: Jennings, Amy
Cc: Adeolu, Abolade
Subject: Dapagliflozin proposed PI and MG
Importance: High

Dear Amy,

Please find attached our first round of comments and edits to the package insert and medguide for dapagliflozin. We will send comments/edits to the carton and container labels once we receive them.

A final regulatory decision has not yet been made, and it is possible that additional edits will be requested after further review by the signatory authority and others.

We encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website. There is a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from the labeling regulations and guidances. We encourage you to use the SRPI checklist as an (internal) quality assurance tool each time you submit your proposed PI.

Please confirm receipt of this email, and let me know if you have any questions. We expect responses from you by noon on Monday, December 23, 2103.

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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Dapagliflozin NDA 202-293 Post-Marketing Requirements (PMRs)

PMR	Final Protocol Submission	Study Completion (Defined as *)	Final Report Submission
<p>Enhanced Pharmacovigilance An assessment and analysis of all foreign and domestic spontaneous reports of (b) (4) serious hepatic abnormalities, and adverse pregnancy outcomes in patients treated with dapagliflozin.</p> <p>Expedited reporting for events of (b) (4) serious hepatic events and adverse pregnancy outcomes.</p> <p>The enhanced pharmacovigilance should continue for (b) (4) 5 years for all other events. Annual interim reports should be submitted to the Agency.</p>	December 2014	January 2024	Final Report Submission: September 2024 (Interim Report Submissions: March 2015, March 2016, March 2017, March 2018, March 2019, March 2020, March 2021, March 2022, March 2023)
(b) (4)			
<p>Cardiovascular Outcome Trial (CVOT) - (DECLARE, Study D1693C00001) A randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death)</p>	Final FDA reviewed protocol was submitted 9-May-2013 Final amendment to address FDA AE of special interest noted in PMR by June 2014	June 2019	June 2020

PMR	Final Protocol Submission	Study Completion (Defined as *)	Final Report Submission
<p>observed with dapagliflozin to that observed in the placebo group is less than 1.3.</p> <ul style="list-style-type: none"> AE of special interest to include Complicated UTI and genital Infections that require hospitalizations including pyelonephritis, atypical infections, and multidrug resistant organisms, acute kidney injury, malignancies (specifically breast and bladder cancer), hypovolemia, eGFR over time, liver events, bone fractures, hypersensitivity reactions 	<p>(Draft amendment submitted for FDA review January 2014)</p>		
<p>Observational follow-up on CVOT (DECLARE Study) to capture ^{(b) (4)} bladder cancer events w/80% power to exclude ^{(b) (4)} relative risk assuming a 2-sided confidence interval of 5%.</p>	<p>Final protocol amendment to address this PMR target January 2015</p> <p>(Submit Draft for FDA review by June 2014)</p>	<p>June 2027</p>	<p>Mar 2028</p>
<p>Rodent Bladder Tumor Promotion Study that best simulates Clinical experience including changes in the bladder microenvironment (in situ tumors) and renal function</p>	<p>November 2014</p> <p>(Draft protocol for FDA review by April 2014)</p>	<p>Study (in-life phase) ends 8 months after start - November 2015</p> <p>(Study to start March 2015--4 months after final protocol approval)</p>	<p>August 2016</p>
<p>Pediatric PK/PD Study (Study MB102-091) A clinical pharmacology study to evaluate the pharmacokinetics, pharmacodynamics, and safety of dapagliflozin in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus on metformin monotherapy.</p>	<p>Complete Final Protocol submitted 30-Apr-2012</p>	<p>August 2014</p>	<p>August 2015</p>
<p>Pediatric Efficacy /Safety study A 26-week, randomized double-blind, placebo-controlled study, followed by a 26week double-blind, placebo-or active-controlled extension, to evaluate the efficacy and safety of dapagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin and as monotherapy.</p>	<p>August 2015</p>	<p>March 2021</p>	<p>March 2022</p>

* Duration of study for epidemiology studies and LPLV for Clinical Trials

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/s/

ABOLADE ADEOLU
01/08/2014

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, December 20, 2013 12:16 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: Dapagliflozin proposed PI and MG

Importance: High

Dear Amy,

Please find attached our first round of comments and edits to the package insert and medguide for dapagliflozin. We will send comments/edits to the carton and container labels once we receive them.

A final regulatory decision has not yet been made, and it is possible that additional edits will be requested after further review by the signatory authority and others.

We encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website. There is a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from the labeling regulations and guidances. We encourage you to use the SRPI checklist as an (internal) quality assurance tool each time you submit your proposed PI.

Please confirm receipt of this email, and let me know if you have any questions. We expect responses from you by noon on Monday, December 23, 2103.



02/20/2013 12:16 PM
Dapagliflozin mg... 02/20/2013 12:16 PM

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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

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/s/

ABOLADE ADEOLU
12/20/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Monday, December 16, 2013 3:43 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293(dapagliflozin): carton/container labels

Importance: High

Dear Amy,

Please let me know if you already received the following comments from Ms. Tossa from the Office of Surveillance and Epidemiology. If so, please disregard, otherwise advice on when you plan to update.

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. 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.

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
12/16/2013

Adeolu, Abolade

From: Jennings, Amy <amy.jennings@bms.com>
Sent: Thursday, December 05, 2013 4:26 PM
To: Adeolu, Abolade
Subject: RE: dapa tcon

Hi Bola,

Sorry for the delay. I have been in meetings. Please see our summary of the meeting below. Please let me know if you need anything further.

FDA requested a meeting to inform BMS/AZ they would like to disclose both the Complete response Letter (CRL) and the Formal Dispute Resolution Response in their briefing materials for the 12-Dec-2013 dapagliflozin EMDAC. FDA said there may be some challenges in just making these available to the EMDAC members without making them public, but noted they were looking into that option. In an effort to expedite agreement, BMS/AZ stated they accepted disclosure of these 2 documents with the FDA EMDAC briefing materials provided the FDA also includes Section 1 (Executive Summary) and Section 6 (Path Forward) of BMS/AZ's Formal Dispute Resolution Request to provide context of what BMS/AZ "asked" in the dispute resolution request. FDA agreed to include these 2 sections.

BMS/AZ brought forward a few other discussion topics:



Action:

- Amy Jennings to email BMS/AZ's Formal Dispute Request to Bola Adeolu. (done)

Regards
Amy

From: Adeolu, Abolade [<mailto:Abolade.Adeolu@fda.hhs.gov>]
Sent: Thursday, December 05, 2013 4:22 PM
To: Jennings, Amy

Subject: dapa tcon

Importance: High

Hi Amy,

I am waiting on your documentation of the discussion held this morning. Please send asap.

thanks

Bola Adeolu, R.Ph., MS, MBA

Regulatory Project Manager,

CDER/OND

Office of Metabolism and Endocrinology Products

White Oak, Bldg 22, Rm 3239

10903 New Hampshire Avenue,

Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
12/06/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, November 22, 2013 1:08 PM
To: Jennings, Amy (amy.jennings@bms.com); Lamendola, Joseph (joseph.lamendola@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293 (dapagliflozin) Renal Impairment/Failure, Volume Depletion and Hyperkalemia

Dear Amy,

Please provide the following information as soon as possible:

1. On page 131 of the 30-Month Update, we note that compared to the two Placebo-Controlled Pools (i.e., ST and ST+LT), the All Phase 2b and 3 Pool included additional patients (i.e., a total of 1070 patients) with an eGFR <60 mL/min/1.75 m². Using the All Phase 2b and 3 Pool for the 30-MU only, provide tables related to renal impairment/failure and volume depletion similar to the following Tables: 46, 49, 50, 51, 52, 53, 54, 55, 56, 57, and 58 (pages 125-143).
2. Provide Kaplan-Meier curves for time-to-first event of volume depletion (similar to Figure 10, page 139) and time-to-first event for renal impairment/failure using the All Phase 2b and 3 Pool.
3. Using the All Phase 2b and 3 Pool, provide information regarding the occurrence of hyperkalemia and marked laboratory abnormalities (MA) of hyperkalemia in patients with and without events of 1) renal impairment/failure, 2) volume depletion and 3) marked laboratory abnormalities of renal function, and include an assessment of the effects of the use of potassium-sparing diuretics, angiotensin converting enzyme inhibitors and angiotensin receptor blockers on these events.
4. Provide graphs of the mean \pm SE of serum potassium and creatinine concentrations and eGFR over time for each study visit for the two Placebo-Controlled Pools (i.e., ST and ST+LT), All Phase 2b and 3 Pool, and for the dedicated renal impairment study (i.e., MB102029). Please include the dapagliflozin 5 mg, 10 mg and comparator study arms for these graphics.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
11/22/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, October 11, 2013 4:18 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293(dapagliflozin)

Dear Amy,

- Please provide any data you may have on the effect of SGLT2 inhibitors on assays that assess glycemic control using 1,5-anhydroglucitol.
- Indicate whether you have any studies ongoing or planned to study this possible effect.
- Indicate whether your current understanding of this effect would support labeling, and if so, please propose labeling language.

Kindly acknowledge receipt and let me know when to expect your response.

Thanks,
Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
10/11/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, October 09, 2013 2:13 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293

Dear Amy,

Thank you for your recent voicemail in response to the October 4, 2013 information request regarding the dapagliflozin dosing information in your proposed PI. You correctly pointed out that FDA had requested the language regarding the 5 mg dose.

Further, we acknowledge that we may have agreed to include only the 10 mg dapagliflozin dose in the placebo-controlled pool analyses for the 30-month safety update. However, for adequate risk-benefit assessment of your product, it would be helpful to the review team if you could also include data for the 2.5 mg, 5 mg and the pooled dapagliflozin treatment arms (i.e., PLA, DAPA 2.5 mg, DAPA 5 mg, DAPA 10 mg and DAPA TOTAL, similar to presentation of data in the SCS) in the summary tables for the Placebo-Controlled Pool (ST) and the Placebo-Controlled Pool (ST+LT) included in your 30-Month Update Report dated June 10, 2013.

The Tables to update with the 2.5 mg, 5 mg and pooled dapagliflozin data would include: Tables 6, 7, 12, 13, 14, 15, 22, 23, 31, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, and 64.

It will not be necessary to include this same dose breakdown for the “NDA Database Lock”, “SCS”, or the “4-MSU” data, only the “30-MU” and “30 Month Sur Database Lock” data are requested.

Please provide this information as soon as possible in order to minimize delays in the review process.

Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
10/09/2013



NDA 202293

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492-7660

Attention: Amy A. Jennings, PhD
Group Director, Cardiovascular/Metabolics
Global Regulatory & Safety Sciences - US

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated and received December 28, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dapagliflozin Tablets, 5 mg and 10 mg. Please also refer to your Class 2 Resubmission dated and received July 11, 2013.

We also refer to:

- Your initial proprietary name submission dated September 23, 2011, received September 26, 2011, requesting review of your proposed proprietary name, Forxiga;
- Our initial correspondence dated December 8, 2011, finding this proposed proprietary name conditionally acceptable;
- Your submission dated and received July 16, 2013, requesting re-review of your proposed proprietary name, Forxiga;
- August 26, 2013, teleconference between FDA and Bristol-Myers Squibb;
- Your amendment to the initial proprietary name submission, dated and received September 9, 2013, requesting review of your proposed proprietary name, Farxiga;

We have completed our review of the proposed proprietary name, Farxiga, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your July 16, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Abolade (Bola) Adeolu at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/07/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Friday, October 04, 2013 3:59 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293

Dear Amy,

“In the resubmission for dapagliflozin NDA (dated July 11, 2013), your proposed dose in T2DM patients with normal renal function is 5 mg or 10 mg once daily. In your original submission (dated Dec 28, 2010) the proposed dose in these patients was only 10 mg once daily. (b) (4)

We are not able to verify when this change was proposed and what was the underlying rationale. Please provide a detailed rationale for the dosing recommendations proposed in the current prescribing information.”

Please submit your response by COB Wednesday, October 9, 2013

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
10/04/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Wednesday, October 02, 2013 8:38 AM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293 (dapagliflozin)

Dear Amy,

For confirmation of the sample sizes included in your 30-Month Update (10-Jun-2013) please specify the location, dataset name(s) and variable names for the datasets used to identify the following study populations:

All Phase 2b/3 Pool (ST+LT)

1. Dapa Total (N=5936)
2. Placebo (N=3403)

Placebo-Controlled Pool (ST)

3. Dapa 10 mg (N=2360)
4. Placebo (N=2295)

Placebo-Controlled Pool (ST+LT)

1. Dapa 10 mg (N=2026)
2. Placebo (N=1956)

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
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/s/

ABOLADE ADEOLU
10/02/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, September 12, 2013 2:15 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: NDA 202293(dapagliflozin): Information Request
Attachments: Information Request to Applicant - Cancer Table 09-12-13.doc

Dear Amy

This email is to request that you provide the following information:

1. Populate the attached table for the 21 studies included in the 30-month update.
2. Identify other cases of bladder, breast and lung neoplasms and melanomas for studies not included in the 21 studies identified in the Table, and provide the same information for these studies.

Please provide this information by Monday (September 16, 2013)

Thank you, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

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/s/

ABOLADE ADEOLU
09/12/2013

MEMORANDUM OF MEETING MINUTES

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

MEETING DATE: August 26, 2013
LOCATION: WO Bldg 22, Room 4311
TIME: 2:00 P.M. (EST)
APPLICATION: NDA 202293
DRUG NAME: Forxiga (dapagliflozin) Tablets, 5 mg and 10 mg
TYPE OF MEETING: Proprietary Name Teleconference
MEETING RECORDER: Sue Kang

FDA ATTENDEES:

Office of Surveillance and Epidemiology
Reasol Agustin (Safety Evaluator, DMEPA)
Yelena Maslov (Team Leader, DMEPA)
Kellie Taylor (Deputy Director, DMEPA)
Sue Kang (Safety Regulatory Project Manager, OSE)

EXTERNAL ATTENDEES:

Bristol-Myers Squibb
Amy Jennings, US Regulatory Lead
Joe Lamendola, Head US Regulatory
Margo Herron, Global Regulatory Policy
James List, Full Development Lead

MEETING OBJECTIVE:

FDA requested this teleconference to notify the Applicant of our concerns with their proprietary name, Forxiga.

BACKGROUND:

In this review cycle, we have identified that your proposed name Forxiga contains the USAN stem *-fo-*. The USAN stem ‘-fo(s)-’ is reserved for phosphoro-derivatives and therefore not acceptable for this product.

We did not identify the stem during our previous review of Forxiga in NDA (OSE RCM #2011-3563 dated December 5, 2011). This oversight occurred in part because the safety review (conducted by Med ERRS, 2010) submitted in support of your name stated that the name FORXIGA did not present any issues from a USAN perspective. However, we and Med-errs should have recognized the Fo- stem at the beginning of the name as an issue. In Sept 2008, FDA published a concept paper on proprietary names advising industry to not include USAN stems ‘because the USAN stems are intended to indicate a pharmacological or chemical trait of a drug, a single stem will be applicable to multiple drug products. Use of these stems in proprietary names, even when used consistently with the USAN meaning, can result in multiple similar proprietary names and proprietary

names that are similar to established names, thus increasing the chance of confusion among those drugs. To reduce the potential for confusion, USAN stems should not be incorporated into proprietary names.

We recommend that you screen potential proprietary names against the USAN stem list and eliminate those that incorporate USAN stems. Guidance on proprietary name evaluation can be found in *PDUFA Pilot Project: Proprietary Name Review Concept Paper*, available online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072229.pdf>

DISCUSSION POINTS:

- The Agency provided the Applicant with regulatory options on how to proceed with their Proprietary Name Review:
 - Consider changing the ‘o’ in the ‘For’ portion of the name to another vowel (i.e., ‘a’ or ‘u’) making the name, Farxiga or Furxiga. Submit an amendment with the change of the spelling of the name.
 - Withdraw the proposed proprietary name, Forxiga and formally submit an alternate name for our evaluation.
- The Agency stated that the two names, Farxiga and Furxiga have been researched from a safety perspective and are unlikely to be denied from the safety perspective. However, these two names have not been sent to the Office of Prescription Drug Promotion for review from a promotional perspective.
- The Agency stated that there are names on the market currently with USAN names, however, since 2008, the Agency is making a concerted effort to ensure that new proprietary names do not contain USAN stems.
- The Applicant stated their proposed proprietary name, Forxiga, is approved overseas and intended on having a global proprietary name.
- The Applicant asked if the USAN issue would apply if their name was phonetically spelled out, i.e., Phorxiga. The Agency stated that phonetically spelling out the –fo- would avoid the USAN issue, however, this new spelling could result in other safety issues, such as look alike and sound alike issues.
- The Applicant asked if they should submit a Med-ERRS report as part of their amendment. The Agency replied that no report is needed, but a cover letter referencing their Request for Proprietary Name Review and the new name they would like the Agency to review is needed.

Conclusion:

- The Applicant stated they will discuss the outcome of today’s meeting with their full team and inform the Agency of their decision.
- The Agency will get the promotional review of the two names, “Farxiga” and “Furxiga” started.

The meeting ended at approximately 2:26 P.M. (EST).

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/s/

YELENA L MASLOV
09/04/2013



NDA 202293

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences – U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

We acknowledge receipt on July 11, 2013, of your July 11, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We consider this a complete, class 2 response to our January 17, 2013, action letter. Therefore, the user fee goal date is January 11, 2014.

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

Sincerely,

{See appended electronic signature page}

Julie Marchick
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK
07/25/2013

Adeolu, Abolade

From: Adeolu, Abolade
Sent: Thursday, December 13, 2012 3:59 PM
To: Jennings, Amy (amy.jennings@bms.com)
Cc: Adeolu, Abolade
Subject: Dapagliflozin

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Amy,

Below are the responses to your questions sent via email on December 3, 2012.

1. **FDA response question 1a:** *"In your list of planned adverse event (AE) analyses, Section 2.3.1.2, add an analysis of Volume Depletion events (described on page 18) over time. This should include Kaplan Meir plots of events for both placebo and dapagliflozin in the short term and short plus long term placebo controlled pools. In addition, include a separate analysis for the renal impairment study 102029 and a subgroup analysis in the high risk cardiovascular studies D1690C00018 and D1690C00019."*
 - As requested, we will include a summary of time to Volume Depletion events with Kaplan Meir plots. In addition, we will include a separate analysis for volume depletion events for the renal impairment study MB102029 and a analysis for volume depletion in the studies D1690C00018 and D1690C00019 (separately and pooled). *We believe this addresses the Agency's request. Please let us know if it does not.*

FDA Response: Yes this addresses our request.

2. **FDA response question 1b:** *"Your placebo-controlled pooled analyses should not exclude patients that took the 10 mg dose of dapagliflozin. You should include the dapagliflozin dose groups in the placebo-controlled pools that were presented in the NDA SCS. As in the SCS, you should present tabular data separately for 2.5 mg, 5 mg, and 10 mg dapagliflozin dose groups and also include a dapagliflozin total group."*
 - In response to the green text above, we wish to clarify that we do not plan to exclude patients that took the 10 mg dose of dapagliflozin from the placebo-controlled pooled analyses.
 - In response to the orange text above, we wish to clarify that almost all of the new data to be included in the placebo-controlled pools in the NDA resubmission is for patients on dapa 10 mg or placebo. Of the 5 studies providing new data in the placebo-controlled pool in the 30month safety update, no studies provide additional data for the ST and only 1 study, D1690C00006, provides additional data for the LT from subjects on dapa 2.5mg/5mg since the 4-month safety update (15Oct2010). In this study there are 65 and 64 subjects for dapa 2.5mg/5mg arms respectively still on-going at time of the 4MSU data cut, with a maximum additional exposure of 3 months per subject. There is one additional SAE for each arm and no discontinuation due to AE/death. In summary, there is no new data on dapa 2.5 mg and 5 mg in the ST placebo-controlled pool since the initial NDA. There will be very limited new data on dapa 2.5 mg and 5 mg in the ST+LT placebo-controlled pool: Less than 4 patient-year additional exposure on top of 867 to 977 patient-year exposures from 4MSU for dapa 2.5mg and 5mg arms, comparing with additional ~ 1160 patient-year exposure on top of 921 to 1107 patient-year exposures from 4MSU for placebo and dapa 10 mg arms. Therefore, we consider the safety assessment across dapa doses (2.5 mg, 5 mg, 10 mg, dapa total) is more appropriately viewed in the initial NDA and the 4-month safety update vs. including them in the 30 month safety update where almost all of the new information is on the dapa 10 mg dose and placebo. *Considering this further clarification, does the Agency agree with BMS/AZ*

proposal to include only the 10 mg dose in the placebo controlled pool for the 30 month safety update?

FDA Response: Yes, we agree.

3. **FDA response question 1d:** *“You should include all completed CSRs that support this NDA, unless they have been previously submitted. It is acceptable not to submit datasets for these supportive studies.”*

- As requested, we will submit CSRs for most of the supportive studies listed in Section 2.1.1 of the NDA resubmission plan document. (b) (4)



FDA Response: Yes, we agree.

4. **New question to FDA related to datasets:** We are planning to use the same version of cDISC that we have been using thus far for dapa NDA 202-293 (i.e. SDTM IG 3.1.2). We understand that there is now a new version of cDISC (i.e. version SDTM 1.2/SDTM IG 3.1.2 Amendment 1). We would prefer to use the same version as our previous submission (i.e. SDTM IG 3.1.2) for consistency. *Does the Agency agree that BMS/AZ will use cDISC version SDTM IG 3.1.2 for the datasets included in the NDA resubmission?*

FDA Response: Yes, we agree

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
12/27/2012



NDA 202293

GENERAL ADVICE

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We refer to your June 27, 2012, submission, containing a request for an extension in which to resubmit the application, in the form of a response to our complete response letter dated January 17, 2012. We also refer to your email dated November 27, 2012, requesting an extension to resubmit the application by July 2013.

We agree with your request for the extension to resubmit this application in July 2013. We remind you that per 21 CFR 314.110(c), an applicant's failure to resubmit the application within the extended time period or to request an additional extension may be considered a request by the applicant to withdraw the application.

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

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
11/28/2012

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, November 27, 2012 11:23 AM
To: Adeolu, Abolade
Subject: RE: Dapagliflozin

Hi Bola;

Thanks! I have a few questions.

- RE your request in response to comment 1, *“Send a table of all the studies that you plan to use to support the resubmission NDA as described in your Pre-NDA briefing package. This table should include all the categories seen in your NDA Summary of Clinical Safety (SCS) Table 1 (description, status, population, N, duration, treatment, rescue, efficacy assessment). Indicate in this table which studies are considered core studies for the resubmission NDA and which are considered supportive studies. Also indicate which are extension/long term data studies. Please submit this table within two weeks.”* I see the letter is dated Nov 19 . It will be hard for us to get this table to you by Monday of next week because we just received your letter today. **Are you ok if we provide by 2 weeks from today (i.e., 11-Dec-2012)?**
- RE your response to our question in the cover letter of this submission (response #4 in your letter), *“Yes, we will likely grant the request. However, you will need to submit a formal request for this extension.”* I am a little confused on what is needed. We did submit a formal request for an NDA resubmission extension (submitted 27-Jun-2012, NDA 202-293/SN0084--attached) and then again formally requested the extension with the question in the cover letter with the 26-Oct-2012 (NDA 202-293/SN0088) submission *“To follow-up on the NDA resubmission extension request submitted 27-Sep-2012 (NDA 202-293/SN0084). At the time of that request it was not clear how long of an extension we would need. If the Agency endorses the proposed resubmission plan included with this submission, we target to resubmit the dapagliflozin NDA end-June/early-July 2013. As such, we request an extension to resubmit the NDA to July-2013. Does the Agency grant this extension request?”* **Can you please let me know what I need to do to formally request this extension?**

Thanks
Amy

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/s/

ABOLADE ADEOLU
11/28/2012



NDA 202293

GENERAL ADVICE

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to your October 26, 2012, submission, containing request for advice on your proposed NDA resubmission.

You requested responses to the following questions. The questions are repeated below, followed by our responses in **bold** font.

1. BMS/AZ consider the plan outlined in this document to be in line with the path forward put forth by the Agency in the [complete response letter] CRL and Dispute Decision and sufficient for a resubmission of the dapagliflozin NDA.
 - a. Does the Agency agree with the planned studies/data to be included with this NDA resubmission as described in Section 2.1? If not, what additional information is the Agency looking to be included in this resubmission?

FDA Response:

Your resubmission plan is consistent with what has been requested with the CR letter as well as the Appeal Denied Letter. We have the following additional requests:

Send a table of all the studies that you plan to use to support the resubmission NDA as described in your Pre-NDA briefing package. This table should include all the categories seen in your NDA Summary of Clinical Safety (SCS) Table 1 (description, status, population, N, duration, treatment, rescue, efficacy assessment). Indicate in this table which studies are considered core studies for the resubmission NDA and which are considered supportive studies. Also indicate which are extension/long term data studies. Please submit this table within two weeks.

In your list of planned adverse event (AE) analyses, Section 2.3.1.2, add an analysis of Volume Depletion events (described on page 18) over time. This should include Kaplan Meir plots of events for both placebo and dapagliflozin in the short term and short plus long term placebo controlled pools. In addition, include a separate analysis for the renal impairment study 102029 and a subgroup analysis in the high risk cardiovascular studies D1690C00018 and D1690C00019.

- b. Does the Agency agree with the pooling plan for safety evaluation (as described in Section 2.3.1.1) and planned safety analyses for the pooled data (as described in Section 2.3.1.2)?

FDA Response:

Your placebo-controlled pooled analyses should not exclude patients that took the 10 mg dose of dapagliflozin. You should include the dapagliflozin dose groups in the placebo-controlled pools that were presented in the NDA SCS. As in the SCS, you should present tabular data separately for 2.5 mg, 5 mg, and 10 mg dapagliflozin dose groups and also include a dapagliflozin total group.

- c. Does the Agency agree with our plan to provide individual study data safety analyses as described in Section 2.3.1.3?

FDA Response:

Yes, we agree.

- d. Does the Agency agree with our proposal not to include [clinical study reports] CSRs and datasets for some of the supportive studies as described above and in Sections 2.3.1.3?

FDA Response:

You should include all completed CSRs that support this NDA, unless they have been previously submitted. It is acceptable not to submit datasets for these supportive studies.

2. Is the Agency willing to meet with BMS/AZ to discuss the scope of the planned advisory committee meeting and the expertise that will comprise the advisory committee panel?
We understand that we will need to submit an official meeting request.

FDA Response:

The Division has not, to date, conducted meetings of this nature with sponsors. While you may submit an official meeting request, it is unlikely that we would grant your request.

3. After we have data from the ongoing studies that follow the precedent established by prasugrel, is the Agency willing to meet with BMS/AZ to review these data and discuss if these data adequately address the need for additional nonclinical work?

FDA Response:

We request that the study report be submitted for our review prior to any potential meeting to discuss the data. Given the pharmacology of dapagliflozin, we maintain that a bladder tumor promotion model where the anatomic site and cellular environment most closely resembles the human condition, such as the hydroxybutyl nitrosamine (BBN) model, could be more informative than the proposed xenograft model where tumorigenesis and the tumor environment depends on the injection site (orthotopic vs heterotopic). Recent publications^{1,2} have addressed critical attributes of orthotopic rodent models, including the observation of similar gene expression profiles across rat, mouse, and human bladder tumors². Results from either model, however, will be accepted and reviewed with consideration given to the strengths and limitations of your chosen model.

¹Eijan AM, Lodillinsky C and Sandes EO (2102). Animals Models for Basic and Preclinical Research in Bladder Cancer. Bladder Cancer - From Basic Science to Robotic Surgery, Canada, A (Ed.)

²Lu, Y et.al.; Am. J. Transl. Res.: 3(1):8-27 (2011)

4. To follow-up on the NDA resubmission extension request submitted 27-Sep-2012 (NDA 202-293/SN0084). At the time of that request it was not clear how long of an extension we would need. If the Agency endorses the proposed resubmission plan included with this submission, we target to resubmit the dapagliflozin NDA end-June/early-July 2013. As such, we request an extension to resubmit the NDA to July-2013. Does the Agency grant this extension request?

FDA Response:

Yes, we will likely grant the request. However, you will need to submit a formal request for this extension.

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

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
11/19/2012



NDA 202293

DISPUTE APPEAL – DENIED

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to your July 17, 2012, request for formal dispute resolution, received on July 17, 2012, to the Office of New Drugs. The request for dispute resolution concerns the deficiencies described in the January 17, 2012, Complete Response letter (CRL) from the Office of Drug Evaluation II (ODE II). Specifically, as quoted from your submission, you propose 1) that the CV data from studies D1690C00018 and D1690C00019 be viewed in the context of the overall CV risk assessment of dapagliflozin and not as stand-alone studies, and 2) that the overall benefit/risk assessment of dapagliflozin recognize the demonstrated benefits of dapagliflozin on glycemic control, weight loss and reduction in blood pressure (BP), as well as the questionable and scientifically improbable risks pertaining to bladder cancer and liver safety. We also refer to the meeting held between FDA and BMS on August 15, 2012, where the issues raised in your request for formal dispute resolution were discussed.

The following excerpt from the CR letter provides context:

While we cannot conclude that dapagliflozin is associated with an excess CV risk based on an analysis of only these two trials [Studies D1690C00018 and D1690C00019], the findings from these two large, adequate and well-designed trials in a relevant patient population cannot be ignored. More importantly, we cannot include any suggested CV benefit observed in the original meta-analysis in a risk-benefit consideration in regard to cancer and liver safety signals.

Furthermore, while the glucose-lowering effect of dapagliflozin is the result of a novel mechanism of action that does not rely on insulin secretion or insulin sensitivity, the achieved HbA1c reductions are modest, and attenuated or absent in patients as renal function decreases. An anti-diabetic therapy that is ineffective in patients with moderate to severe renal impairment is a major limitation as many patients with T2DM have or will develop renal impairment.

Overall, the observed clinical benefits of dapagliflozin in your current clinical development program may be achieved with other available anti-diabetic therapies. In the absence of a unique benefit of

dapagliflozin over these other therapies, an unmet need that may be filled by dapagliflozin could not be identified to offset potential risks of bladder cancer and hepatic toxicity.

The path forward outlined in the CRL stated that you would need to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, that must include patients from Studies 18 and 19, studies enriched for high CV risk patients who have completed at least 52 weeks of the trials. It would be expected that these analyses would include updated information on bladder cancer events and new risk estimates; an updated review of hepatic safety, and; an updated CV meta-analysis including an analysis of MACE events. You were strongly advised to initiate your planned large CV outcomes trial.

I reviewed this Formal Dispute Resolution Request (FDRR) and the data, rationale and decision making underlying the CR action on this NDA at length. I have met with the review team on several occasions, as well with you. In all of those meetings I have appreciated the insights and perspective contributed by Dr. John Jenkins, Director of the Office of New Drugs, Dr. Robert Temple, Deputy Center Director for Clinical Science, and Dr. Lisa LaVange, Director of the Office of Biostatistics. I have also discussed the bladder cancer cases with Dr. Richard Pazdur, Director, Office of Hematology and Oncology Products.

I will address the two points of dispute raised in this FDRR in reverse order.

1. BMS/AZ propose that the overall risk/benefit assessment of dapagliflozin recognize the demonstrated benefits of dapagliflozin on glycemic control, weight loss, and reduction in blood pressure (BP), as well as the questionable and scientifically improbable risk pertaining to bladder cancer and liver safety.

The FDA review team has recognized the benefits of dapagliflozin on glycemic control, weight loss and reduction in blood pressure. I agree with the team that efficacy of dapagliflozin is modest, although I don't find that a negative in any way. Given the drug's clinical pharmacology it is likely to be best utilized in patients who are relatively early in the course of their diabetes and have not yet developed renal impairment. The FDA team also agreed that there appears to be added value in the drug's ability to lead to weight loss and lower blood pressure as well as its novel mechanism of action. However, with many options in that armamentarium such added value is difficult to quantify and balance against dapagliflozin's limitations of use, including in patients with renal impairment and teratogenicity, an important considerations for patients who are women of child bearing age. In reading the FDA reviews for the NDA, it is clear to me that the team did take into full account the benefits outlined in this FDRR. Such benefits are always difficult to quantify against potential risks.

The crux of the NDA decision rested in balancing the full constellation of efficacy and safety concerns, including liver toxicity, bladder cancer and CV safety. As noted above, like most of the FDA review team, I do not find the single case of severe hepatotoxicity in the NDA database, which was complicated by features of autoimmune hepatitis, as concerning as it would be in the setting of a strong signal of transaminitis among dapagliflozin patients (Hy's Law). It does not absolve the drug of any hepatotoxic risk, but I do not find that it sounds the alarm for high risk of liver toxicity that might result in transplant or mortality.

With regard to cancer risk, all FDA reviewers came to the conclusion that the original concerns about breast cancer risk were likely unfounded; again, I agree. Of note, these assessments were influenced

by additional data in the NDA that were submitted after the Endocrinologic and Metabolic Drugs Advisory Committee July 19, 2011, meeting. This leaves bladder cancer to be considered and while most reviewers agreed that risk is likely to be low, it did serve as a major focus in the CR letter and among the AC members. My assessment is that when the time came to vote at the AC meeting, the members really focused on the combined picture of breast cancer and bladder cancer.

I am less concerned that the bladder cancer cases represent an important signal of risk than most of the FDA reviewers. Most of the cases occurred too early during treatment (less than 6 months) to be realistically considered related to drug exposure or the patients had clear clinical suggestions of disease (hematuria) upon study entry. The cases, along with the epidemiology of the bladder cancer, confirm the reassurance provided by the preclinical data that the likelihood dapagliflozin is a carcinogen or tumor promoter is low. Nonetheless, there remains residual concern that something is amiss in the fact that the treatment and control patients had the same rates of baseline hematuria and I expect the shadow cast on the drug from the originally large number of bladder cancer cases will be difficult to erase. I am hopeful that additional follow-up data from continuations of dapagliflozin clinical trials, including Studies 18 and 19 given their large size, will add further reassurance, but dropouts may affect that. Also, a study of dapagliflozin in a tumor promotion model that closely mimics clinical use of the drug and targets transitional bladder cells will go a long way to providing reassurance about any potential risk. Finally, your postmarketing safety studies should include careful assessment for bladder cancer incidence.

2. BMS/AZ propose that cardiovascular (CV) data from studies D1690C00018 and D1690C00019 be viewed in the context of the overall CV risk assessment of dapagliflozin and not as stand-alone studies.

Discussions about assessing CV risk of dapagliflozin in this FDRR with the review team and Drs. Jenkins, Temple and LaVange have been rich and lively. You essentially contend that Studies 18 and 19 should not be considered as a “sub” meta-analysis, but rather as contributing to the overall body of data in the updated meta-analysis. In reality, one can not ignore results of individual studies, but must take those findings into account in reviewing the totality of data. The overall, updated meta-analysis that included these two studies continued to meet the boundaries set by the FDA Guidance on assessing CV risk for diabetes treatments. What it did not do was confirm a CV benefit that all were looking for in requesting that update. Instead, it raised new concerns about CV risk.

The CR letter does not hold you to a requirement based on the results of that sub-meta-analysis as if it were all that mattered, which the FDRR subtly implies. If that had been the case, the CRL would have advised that your planned large CV outcomes safety study was required before marketing, since the upper bound of 95% CI around the Hazard Ratio for MACE + UA exceeded 1.8. Instead, the CRL stated that you should resubmit the NDA when at least 52 weeks of data from Studies 18 and 19 were analyzed, which you subsequently indicated would not alter these rates; the 2 year mark for the studies closure may be more informative and is imminent.

Once in hand, it was appropriate for the FDA review team to consider the independent value added by the interim analyses of studies 18 and 19 in assessing the totality of the evidence about dapagliflozin. Highly enriched for CV risk, they do burst the bubble of hope that dapagliflozin confers CV benefit, at least not once other CV risk factors are operative. They also lead one to think further about what population of T2DM patients is most likely to benefit, but avoid risk, in using the drug especially since the efficacy of dapagliflozin diminishes as renal function declines. It is reassuring that the time to

event curves for Studies 18 and 19 alone show rapid divergence in the first few months and then remain steadfastly parallel. Similarly, the exploratory analysis by FDA reviewers that adds in high risk patients from the rest of the database shows remarkably congruent time to event curves for the treatment and control patients, diverging at about months 8 to 10 in favor of dapagliflozin. However, the studies raise more questions about CV risk than they were expected to. The request for additional follow-up data pre-approval from the studies that raised these questions is appropriate.

DECISION AND PATH FORWARD

Your FDRR proposes that dapagliflozin should be approved based on the data already submitted to the NDA and that CV benefit should not be required to outweigh the weak signals of toxicity. You also state your continued commitment to conduct a large CV outcome trial and a large pharmacoepidemiology study to definitively quantify the CV risk profile of the drug and assess cancer and hepatotoxicity risks.

For the reasons stated above, your proposed path forward is denied.

1. **The path forward as written in the CR letter is reasonable under the circumstances posed by the data in the NDA and stands as written.** This includes the request for updated safety analyses of the NDA database, including at least 52 weeks of data from Studies 18 and 19, but given information that you shared with the review team about event rates at 52 weeks, the full study data, which are expected to be completed with two years of data are imminent and would be far preferable. Even if there are many patients who have left the study, it is important that as much data from it as possible be brought to consideration, as should additional information about the patient with concerning liver disease, which was included in this FDRR but is considered new data so has not been reviewed by me.
2. **A resubmitted NDA should be brought before an Advisory Committee.** A second AC meeting on this drug is important because data and the overall spectrum of risk have shifted since their first meeting. Additional data about liver toxicity and breast cancer were brought to bear in the major amendment from the first cycle of the NDA, lessening the concern for some risk signals that were of concern when the AC convened and those data have continued to accumulate. More importantly, the CV data and how it evolved to shift expectations for dapagliflozin, from having hope for CV benefit to concern about a signal of CV risk, warrants discussion. It raises questions about how to factor in new data to a meta-analysis that has already been used to make a decision, that the FDA Guidance on CV risk for diabetes drugs does not fully address. Also, how should clinical trials that are highly enriched for CV risk be considered in the overall premarketing risk assessment for a diabetes treatment? If they are to play a major role, should such enriched trials be required earlier in development than was planned for dapagliflozin? Should they carry more weight than studies in patients with fewer CV risk factors? These questions, being raised in the context of this NDA, should not be answered without public discussion.
3. **You must conduct a preclinical toxicology study to address the issue of tumor promotion of bladder cancer, even in light of the reduced number of cases of concern in the database.** The balanced rates of baseline hematuria across dapagliflozin patients and controls diminish the light of the reduced number of cases of individual concern in the database. This study is

reasonable to conduct in the postmarketing period, unless the review of the resubmitted NDA raises new concerns about bladder cancer. Per FDA pharmacology/toxicology experts, the most relevant model would be one that evaluates the effect of dapagliflozin on transitional cell tumor growth within the bladder. There are several models that would allow for this, as they best reflect the human clinical experience – a change in urinary composition and renal function from dapagliflozin and transitional tumors in the bladder. I believe that if such a study is negative it may serve to greatly lessen residual concerns about bladder cancer risk.

Questions regarding next steps as described in this letter should be directed to Abolade Adeolu, Senior Regulatory Project Manager, at (301) 796-4264.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

RADM Sandra L. Kweder, M.D.
United States Public Health Service
Deputy Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

SANDRA L KWEDER
09/14/2012



NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to the meeting between representatives of your firm and the FDA on August 15, 2012. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution we received on July 17, 2012.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4842.

Sincerely,

{See appended electronic signature page}

Larry Bauer
Senior Regulatory Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Formal Dispute Resolution

Meeting Date and Time: August 15, 2012. 10:30 am - 12:00 pm EST
Meeting Location: White Oak Campus, Building 22, room 1415

Application Number: NDA 202293
Product Name: Dapagliflozin tablets (5 and 10 mg).
Sponsor/Applicant Name: Bristol-Myers Squibb

Meeting Chair: RADM Sandra L. Kweder, M.D.
Meeting Recorder: Larry Bauer

FDA ATTENDEES

Office of New Drugs

John Jenkins, M.D., Office Director

RADM Sandra L. Kweder, M.D, Deputy Office Director

Larry Bauer, Senior Regulatory Project Manager, Regulatory Affairs Team

Office of New Drugs/Office of Drug Evaluation II

Curtis Rosebraugh, M.D., M.P.H., Office Director

Mary Parks, M.D., Director, Division of Metabolism and Endocrinology Products

Somya Dunn, M.D., Medical Officer, Division of Metabolism and Endocrinology Products

Julie Marchick, M.P.H., Supervisory Project Manager, Division of Metabolism and Endocrinology Products

Mehreen Hai, Ph.D., Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products

Bola Adeolu, R.Ph., MS, MBA, Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products

Office of Translational Science/Office of Biostatistics

Lisa Lavange, Ph.D., Office Director

Thomas Permutt, Ph.D., Director, Division of Biometrics VII

Aloka Chakravarty, Ph.D., Director, Division of Biometrics VII

Matt Soukup, Ph.D., Team Leader, Division of Biometrics VII

Center for Drug Evaluation and Research

Robert Temple, M.D., Deputy Center Director for Clinical Sciences

SPONSOR ATTENDEES

Bristol-Myers Squibb

Mathias Hukkelhoven, PhD, Senior Vice President, Global Regulatory and Safety Sciences

Joe Lamendola, PhD, Vice President, US Regulatory Head, Global Regulatory and Safety Sciences

Amy Jennings, PhD, Director, US Regulatory, Global Regulatory and Safety Sciences

Brian Daniels, MD Senior Vice President, Head Global Development & Medical Affairs

Fred Fiedorek, MD, Senior Vice President, Head of CV and Metabolic Development

James List, MD, PhD, Vice President , Development Lead Dapagliflozin

Dominic Labriola, PhD, Vice President, Global Biometric Sciences

AstraZeneca

Peter Honig, MD, MPH, Vice President, Global Regulatory Affairs

Howard G. Hutchinson, MD, FACC Chief Medical Officer AZ

1.0 BACKGROUND

Bristol-Myers Squibb (BMS) submitted a formal dispute resolution request to the Office of Drug Evaluation II (ODE II) on July 17, 2012 concerning the complete response action taken on January 17, 2012 for dapagliflozin. The proposed indication is to improve glycemic control in adults with type 2 diabetes mellitus. An End-of-Review (EOR) meeting was held with the sponsor on April 30, 2012. The issues to be resolved in this dispute resolution include the sponsor's proposal that the cardiovascular (CV) data from studies D1690C00018 and D1690C00019 be viewed in the context of the overall CV risk assessments of dapagliflozin and not as stand-alone studies. They also request that the overall benefit/risk assessment of dapagliflozin include the demonstrated benefits on glycemic control, weight loss, and reduction in blood pressure as well as the potential risks of bladder cancer and liver toxicity. Dr. Sandra Kweder from the Office of New Drugs is the deciding authority.

2.0 MEETING OBJECTIVES

The objective of this meeting was to discuss the issues surrounding the appeal.

3.0 DISCUSSION

Bristol-Myers Squibb presented a series of slides used throughout the meeting including the following topics:

- Benefit, risks, and certainty assessments comparing dapagliflozin (SGLT2 Inhibitor) to approved incretin-based drugs
- Data showing the distribution of tumor incidence across organ systems and study arms. A discussion ensued exploring the bladder cancer signal in the treatment arm.
- Extended data and medical history from the 78 year-old patient that had developed liver toxicity.
- The inclusion of all of their studies in the meta-analysis for CV risk, not just studies D1690C00018 and D1690C00019, was proposed in their original statistical plan
- BMS proposed a path forward including a Complete Response to the CRL, including currently available information and ^{(b) (4)} post-marketing commitments:

^{(b) (4)}

4.0 DECISIONS (AGREEMENTS) REACHED

This meeting was not conducted with the expectation that decisions would be made or agreements reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request which will be made in 30 days from the meeting date.

5.0 ATTACHEMENTS

Slides from the BMS presentation.

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/s/

LARRY J BAUER
09/14/2012

RECORD OF TELEPHONE CONVERSATION/MEETING	DATE: 06.09. 2012						
<p>Background: FDA sent this comment to applicant on 08.27.2012 and the sponsor requested a tcon to review this recommendation:</p> <p>Thank you for submitting the EMA safety working party (SWP) evaluation of the nonclinical carcinogenicity data. We agree with the SWP that "the putative human tumourigenic activity of dapagliflozin in the bladder is expected to be due to (underlying) tumor promotion and not induction". We recognize that results of an <i>in vivo</i> tumor promotion study alone would not definitively resolve the clinical signal, but would rather contribute to the weight of evidence regarding the biologic plausibility of the clinical signal.</p> <p>To this end, we believe that results from such a study could be informative. Therefore, we recommend that you consider a study in a rodent bladder tumor promotion model using 4-hydroxybutyl(butyl)nitrosamine (OH-BBN) as the initiator.</p> <p>Discussion:</p> <div style="background-color: #cccccc; height: 400px; width: 100%; margin-top: 10px;"> (b) (4) </div>	<p>NDA NUMBER: 202293</p> <p>PRODUCT NAME: Dapagliflozin</p> <p>FIRM NAME: BMS</p> <p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 60%;">Dr. Amy Jennings</td> <td>Director, Global Regulatory Sciences</td> </tr> <tr> <td>Dr. Mike Graziano</td> <td>Vice President, Drug Safety Evaluation</td> </tr> <tr> <td>Tim Reilly</td> <td>Director, Drug Safety Evaluation</td> </tr> </table> <p>TELEPHONE NUMBER:</p> <div style="background-color: #cccccc; width: 100px; height: 15px; margin-top: 5px;"> (b) (4) </div>	Dr. Amy Jennings	Director, Global Regulatory Sciences	Dr. Mike Graziano	Vice President, Drug Safety Evaluation	Tim Reilly	Director, Drug Safety Evaluation
Dr. Amy Jennings	Director, Global Regulatory Sciences						
Dr. Mike Graziano	Vice President, Drug Safety Evaluation						
Tim Reilly	Director, Drug Safety Evaluation						

(b) (4)

SIGNATURE: Todd Bourcier, Ph.D.
Pharmacology Supervisor

DIVISION: DMEP/HFD-510

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/s/

MUKESH SUMMAN
09/07/2012

TODD M BOURCIER
09/07/2012
tcon minutes

From: Adeolu, Abolade
Sent: Monday, August 27, 2012 11:55 AM
To: 'Jennings, Amy'
Cc: Adeolu, Abolade
Subject: NDA 202293 (dapagliflozin)

Dear Amy,

Thank you for submitting the EMA safety working party (SWP) evaluation of the nonclinical carcinogenicity data.

We agree with the SWP that "the putative human tumourigenic activity of dapagliflozin in the bladder is expected to be due to (underlying) tumor promotion and not induction". We recognize that results of an *in vivo* tumor promotion study alone would not definitively resolve the clinical signal, but would rather contribute to the weight of evidence regarding the biologic plausibility of the clinical signal. To this end, we believe that results from such a study could be informative. Therefore, we recommend that you consider a study in a rodent bladder tumor promotion model using 4-hydroxybutyl(butyl)nitrosamine (OH-BBN) as the initiator.

Please contact me if you have any questions.

Regards,
Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
08/27/2012

From: Adeolu, Abolade
Sent: Thursday, August 16, 2012 10:16 AM
To: 'Jennings, Amy'
Cc: Adeolu, Abolade
Subject: NDA 202293 (dapagliflozin)

Follow Up Flag: Follow up
Flag Status: Blue

Dear Amy,

At your Formal Dispute meeting with FDA on August 15, 2012, you presented additional information on Case D1690C00004-4402, the one patient in your clinical trial database who presented with marked transaminase and bilirubin elevations while on dapagliflozin therapy. Please provide a detailed narrative of this patient's clinical course since discontinuation from the trial. Include in this narrative a timeline of hepatic enzymes and other hepatic laboratory studies, concomitant medications (dose, date of initiation and discontinuation), and written assessments by your expert hepatologists.

Please submit the narratives for all the prostate cancer cases.

Please submit a copy of the label that will be used in the EU for dapagliflozin.

Thanks, Bola

Bola Adeolu, R.Ph., MS, MBA
Regulatory Project Manager,
CDER/OND
Office of Metabolism and Endocrinology Products
White Oak, Bldg 22, Rm 3239
10903 New Hampshire Avenue,
Silver Spring, MD 20993

Tel: 301 796-4264

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/s/

ABOLADE ADEOLU
08/16/2012



NDA 202293

**ACKNOWLEDGE DISPUTE APPEAL AND
MEETING GRANTED**

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We acknowledge receipt on July 17, 2012, of your request for formal dispute resolution concerning the January 17, 2012, Complete Response letter to NDA 202293. Specifically, how the cardiovascular safety and benefit/risk profile were assessed. You are requesting that the NDA be approved based on the current data and that no additional clinical trial data is necessary for approval.

Your appeal has been forwarded for review to RADM Sandra L. Kweder, M.D, Director, Office of New Drugs (OND), Center for Drug Evaluation and Research. In your appeal you request a meeting to discuss the matter. We are granting your meeting request and have scheduled the following meeting.

Date: August 17, 2012
Time: 9:30 am – 11:00 am, EST
Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room 1315
Silver Spring, MD 20903

CDER participants (invited):

Office of New Drugs

John Jenkins, M.D., Office Director
RADM Sandra L. Kweder, M.D, Deputy Office Director
Amy Bertha, Team Leader, Regulatory Affairs Team

Office of New Drugs/Office of Drug Evaluation II

Curtis Rosebraugh, M.D., M.P.H., Office Director
Leah Ripper, Associate Director for Regulatory Affairs
Mary Parks, M.D., Director, Division of Metabolism and Endocrinology Products
Jean-Marc Guettier, M.D., Team Leader, Division of Metabolism and Endocrinology Products
Somya Dunn, M.D., Medical Officer, Division of Metabolism and Endocrinology Products
Julie Marchick, M.P.H., Supervisory Project Manager, Division of Metabolism and Endocrinology Products

Mehreen Hai, Ph.D., Regulatory Health Project Manager, Division of Metabolism and Endocrinology Products

Office of Translational Science/Office of Biostatistics

Lisa Lavange, Ph.D., Office Director

Matt Soukup, Ph.D., Team Leader, Division of Biometrics VII

Center for Drug Evaluation and Research

Robert Temple, M.D., Deputy Center Director for Clinical Sciences

Please e-mail me a list of your attendees at amy.bertha@fda.hhs.gov. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Please use the visitor main entrance in building 22. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Amy Bertha at (301) 796-1647 or Charmaine Johnson at the OND Immediate Office main number (301) 796-0700.

Subsequent to the meeting, we will respond to the formal dispute request within 30 days of the meeting (September 16, 2012). We will contact you should we have any questions or require additional information. If you have any questions please call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Team Leader, Regulatory Affairs Team
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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

/s/

AMY E BERTHA
07/31/2012



NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 30, 2012. The purpose of the meeting was to have a high-level discussion on the benefit/risk required for diabetes drugs as well as how the Agency views the need for new classes of drugs versus the known benefits/risks of existing drug classes.

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: April 30, 2012, 1:30 – 2:30 p.m.
Meeting Location: White Oak Campus, Silver Spring, MD

Application Number: NDA 202293
Product Name: Dapagliflozin tablets
Indication: Treatment of type 2 diabetes mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb (in collaboration with Astra-Zeneca)

Meeting Chair: John K. Jenkins, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Janet Woodcock, M.D.	Director, Center for Drug Evaluation and Research
John Jenkins, M.D.	Director, Office of New Drugs
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Julie Marchick, M.P.H.	Regulatory Project Manger, DMEP

SPONSOR ATTENDEES

<i>Bristol-Myers Squibb (BMS)</i>	
Elliot Sigal	Executive Vice President, Chief Scientific Officer & President, R&D
Mathias Hukkelhoven, Ph.D.	Senior Vice President, Global Regulatory Sciences
Brian Daniels, M.D.	Senior Vice President, Head Global Development & Medical Affairs
<i>AstraZeneca (AZ)</i>	
Howard G. Hutchinson, M.D., FACC	Chief Medical Officer
Peter Honig, M.D., M.P.H.	Vice President, Global Regulatory Affairs
Fred Fiedorek, M.D.	Senior Vice President, Head of CV and Metabolic Development

Meeting Minutes
Type C Meeting

BACKGROUND

Bristol-Myers Squibb (BMS) submitted NDA 202293 for dapagliflozin tablets, a sodium-glucose transporter-2 (SGLT2) inhibitor, being developed for treatment of type 2 diabetes mellitus, on December 27, 2010. On January 17, 2012, a complete response letter issued for NDA 202293.

The sponsor requested a Type C meeting for a high level discussion on the benefit/risk required for diabetes drugs as well as how the Agency views the need for new classes of drugs versus the known benefit/risks of existing drug classes.

DISCUSSION

The sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the sponsor on April 27, 2012, follow in bold font. A summary of the meeting discussion is indicated in italicized font.

At the start of the meeting, Dr. Jenkins reminded BMS and AZ attendees that the terms of the meeting being granted was to discuss high-level concerns related to diabetes drug development. Specific discussions related to dapagliflozin would be deferred until the End-of-Review (EOR) meeting which immediately followed this meeting.

Question 1:

a. Is it the Agency's view that unique benefits will need to be demonstrated for all new potential diabetes drugs that have any imbalance in potentially serious events, especially considering that rare events like potential DILI [drug-induced liver injury] cases would be expected to occur stochastically in registrational clinical programs, even if there were no drug-associated liver toxicity?

FDA Preliminary Response: The FDA strongly supports the development of new safe and effective drugs for the treatment of diabetes, and has not established a requirement that new therapies demonstrate a unique benefit over currently available treatments in order to be approved.

Currently, all new anti-diabetic therapies, excluding injectable insulins, are required to demonstrate glycemic efficacy and meet the thresholds for cardiovascular (CV) safety as outlined in the December 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>). These requirements establish a standard process for all companies to follow; however, benefit-risk (BR) assessment of a new drug does not focus only on glycemic control and CV safety. Should an imbalance in potentially serious events (e.g., drug-induced liver injury) occur in the premarket application, FDA must carefully consider the impact of such events, if a true indication of drug toxicity, especially for an anti-diabetic drug intended for use in a large patient population. As there are many

Meeting Minutes
Type C Meeting

available therapies for type 2 diabetes mellitus (T2DM), FDA would need to carefully evaluate the serious safety signal in making our benefit-risk conclusion for approval.

In evaluating potentially serious safety signals , FDA considers the following: the strength of the signal; the seriousness of the event should the risk be *real*; the ability to mitigate the risk; how that risk changes the BR profile of the drug with consideration of other available therapies; and what additional information can be provided by the applicant to further characterize the potential risk. Further characterization may provide reassurance that the risk is absent (original finding was spurious) or lower than originally observed. Further information may also include evidence that there is a unique clinical benefit to offset the risk.

Meeting Discussion: See combined discussion regarding Questions 1a and 1b under Question 1b.

b. If yes, what are the other unique benefits that the Agency would require, other than reduction of HbA1c?

FDA Preliminary Response: FDA has not established criteria for unique benefits for drugs to treat diabetes and generally relies on agreed-upon efficacy endpoint for consideration of approval. However, in some cases demonstration of a unique benefit over other available therapies may be necessary if a serious safety concern is identified for a drug that results in an unfavorable benefit risk assessment.

What that unique benefit is depends on the investigational agent, the safety concern, the indication, and other available therapies. In some cases FDA may look to evidence that the drug is effective in patients where other available agents are not effective and consider a restricted indication. If the safety concern is very serious and risk is difficult to mitigate through labeling, laboratory monitoring, or patient selection, it may be expected that the drug demonstrate a significant clinical benefit such as a cardiovascular outcomes benefit from a prospectively designed outcomes trial to demonstrate superiority or a trial establishing a reduced risk of end-stage renal failure.

Meeting Discussion:

Benefit: The Agency agrees that there is a continued need for new anti-diabetic drugs because the available treatments cannot be considered to cure the disease. Furthermore, many patients fail single-agent therapy necessitating multiple-drug therapy. While there is no general expectation that anti-diabetic drugs provide benefits other than improving glycemic control, as stated in the preliminary comments, in some cases, demonstration of an advantage over other available therapies may be necessary if a serious safety concern is identified that is not present in available therapies and therefore results in an unfavorable benefit-risk assessment for the investigational agent. BMS/AZ raised the possibility that an anti-diabetic agent that also reduced weight should be considered to offer a unique benefit over available therapies. While the Agency does not disagree with this position, the clinical benefit expected to accompany

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Type C Meeting

weight loss is improvement in cardiovascular risk, so that concern with showing that the risk is not increased would be relevant; CV risk will be discussed during the EOR meeting. (b) (4)

the Agency did cite examples where some anti-diabetic therapies with favorable or neutral effects on weight had labeling describing such effects

Liver: Reference was made to “Guidance for Industry – Drug-Induced Liver Injury: Premarketing Clinical Evaluation”, found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>. The Agency stated that Hy’s law is intended to predict whether a drug that causes hepatocellular injury, generally identified by a rate of aminotransferase (AT) elevation greater than control, is likely to lead to severe drug-induced liver injury (DILI), (death or transplant) . Finding one case of Hy’s law in the clinical trial database is concerning. The sponsor asked whether other drugs with a single case of possible DILI but no transaminase imbalance have been approved by FDA. The Agency stated that even a single case of Hy’s Law with evidence of AT elevation can lead to non-approval but that single cases that were not clearly associated with pure hepatocellular injury (i.e., AT elevation), e.g., that showed some evidence of an obstructive component, were harder to interpret. It is likely that single cases of such ambiguous liver injury had not barred approval in some cases but the Agency could not identify any cases during the meeting. The Agency also noted that drugs with very rare serious hepatocellular injury (e.g., nefazadone) may cause neither AT elevation nor Hy’s Law cases if databases are not large enough. The problem is that premarketing applications must be very large to be absolutely certain that there isn’t any possibility of serious liver injury.

Bladder Cancer: The Agency stated that the challenge faced in reviewing an application in which the database includes a rare, serious event is that to answer the question of whether the event is caused by the drug requires a large amount of data and additional patient exposure. Similar to a concern of DILI, cancer imbalances in premarketing applications are exceedingly difficult to sort out. In some cases, the Agency must look to other mechanistic studies to provide some reassurance that the agent is neither an inducer nor promoter. This information with additional patient-years of exposure may provide the reassurance that the signal is not real or diminishingly low.

Question 2:

Can the Agency provide insight into the criteria they would use to determine when additional studies are required or when to require post-marketing commitments/REMS [risk evaluation and mitigation strategies] vs. when they will seek full characterization of rare safety events and/or unique benefit premarket (e.g., the dapagliflozin CRL [complete response letter])?

FDA Preliminary Response: There are no established criteria because every drug, its indication, development program, and safety/efficacy findings are different.

Meeting Minutes
Type C Meeting

However, a REMS or postmarketing required studies/trials may not be the first consideration to address a serious safety concern without first considering what data can be provided pre-marketing.

Meeting Discussion: This question was not discussed during the meeting.

Question 3

a. Considering the FDA-based regulatory decisions for dapagliflozin based on CV [cardiovascular] data from studies D1690C00018 [entitled “A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28 week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care”] and D1690C0019 [entitled “A 24- week multicentre, randomized, double-blind, age stratified, placebo-controlled Phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycaemic control on usual care”] only, instead of the CV meta-analysis from all Phase 2b and dapagliflozin studies, do the sponsors of diabetes drugs need to consider the hazard ratios (HRs) from all individual studies in the future, or can sponsors continue to rely on the HRs derived from the meta-analysis of all studies when assessing CV safety?

FDA Preliminary Response: We will defer the specific discussion on dapagliflozin until the 2:30 p.m. End-of-Review meeting.

Meta-analyses of multiple clinical trials (instead of a single, dedicated cardiovascular outcomes trial) are a collection of heterogenous trials in size, duration, design, patient population and other factors. And while it is not required that every clinical trial in a meta-analysis meets a regulatory threshold of 1.8 in the premarket application, it is important to consider the consistency of effects across these trials.

Meeting Discussion: See combined discussion of Question 3a and 3b under Question 3b.

b. The current FDA CV guidance [Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes] recommends looking across the entire clinical program for evidence of no CV risk. Are we now being asked to look at specific subgroups of patients? And if so, BMS/AZ consider that patients within that subgroup with appropriate risk factors should come from entire program and not just limited to a couple of studies. Does the Agency agree? If not, can the Agency provide rationale for their position?

FDA Preliminary Response: The Guidance specifically states that “the report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings”. FDA has always requested

Meeting Minutes
Type C Meeting

analyses by subgroups to determine consistency of overall findings and also identified areas of concern which may warrant further evaluation. Please see response to Question 3a on characteristic of a meta-analysis which further underscores the importance of looking at subgroups with the meta-analysis.

Meeting Discussion: The Agency stated that because a randomized clinical trial is generally considered the best way to describe the true effects of a drug, the further a study design is from a randomized clinical trial, the less confident the Agency can be in the results. The Agency is working on a guidance describing best approaches to conducting and analyzing meta-analyses, but this guidance is not ready for publication at this time. It was also noted that it is common practice for the Agency to look carefully at consistency of findings from relevant studies contributing to the overall meta-analysis results.

ATTACHMENTS AND HANDOUTS

Slides presented by sponsor at meeting.

3 Page(s) has been Withheld in Full as B4 (CCI/TS)
immediately following this page

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/s/

MEHREEN HAI
05/30/2012



NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to the End-of-Review meeting between representatives of your firm and the FDA on April 30, 2012.

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

If you have any questions, call me, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Review

Meeting Date and Time: April 30, 2012
Meeting Location: White Oak Campus, Silver Spring, MD

Application Number: NDA 202293
Product Name: Dapagliflozin tablets
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb
(in collaboration with Astra-Zeneca)

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Office of the Center Director
Robert Temple, M.D.

Deputy Center Director for Clinical Science

Office of New Drugs

John Jenkins, M.D.
Curtis Rosebraugh, M.D.
Leah Ripper
Mary Parks, M.D.

Director, Office of New Drugs
Director, Office of Drug Evaluation II (ODE II)
Associate Director for Regulatory Affairs, ODE II
Director, Division of Metabolism and
Endocrinology Products (DMEP)
Acting Diabetes Clinical Team Leader, DMEP
Clinical Reviewer, DMEP
Pharmacology/Toxicology Team Leader, DMEP
Pharmacology/Toxicology Reviewer, DMEP
Deputy Director for Safety, DMEP
Regulatory Project Manager, DMEP
Regulatory Project Manager, DMEP

Jean-Marc Guettier, M.D.
Somya Dunn, M.D.
Todd Bourcier, Ph.D.
Mukesh Summan, Ph.D.
Amy Egan, M.D., M.P.H.
Mehreen Hai, Ph.D.
Julie Marchick, M.P.H.

Office of Biometrics

Todd Sahlroot, Ph.D.
Jonathan Norton, Ph.D.

Deputy Director, Division of Biometrics II
Biostatistics Reviewer, Division of Biometrics II

Mat Soukup, Ph.D. Team Leader, Division of Biometrics VII
Bo Li, Ph.D. Biostatistics Reviewer, Division of Biometrics VII
Janelle Charles, Ph.D. Biostatistics Reviewer, Division of Biometrics VII

Office of Clinical Pharmacology

Jaya Vaidyanathan, Ph.D. Acting Team Leader, Division of Clinical
Pharmacology 2

Office of Surveillance and Epidemiology

Diane Wysowski, Ph.D., M.P.H., Team Leader, Division of Epidemiology 1 (DEPI)
Christian Hampf, Ph.D. Pharmacoepidemiologist, DEPI
Lanh Green Team Leader, Division of Pharmacovigilance 1
Amarylis Vega, M.D., MPH Risk Management Analyst, Division of Risk
Management
Margarita Tossa, M.S. Safety Regulatory Project Manager

SPONSOR ATTENDEES

BMS

Mathias Hukkelhoven, Ph.D. Senior Vice President, Global Regulatory and
Safety Sciences
Joe Lamendola, Ph.D. Vice President US Regulatory Head, Global
Regulatory and Safety Sciences
Amy Jennings, Ph.D. Director, US Regulatory, Global Regulatory and
Safety Sciences
Roland Chen, M.D. Vice President, Medical Safety Assessment, Global
Regulatory and Safety Sciences
Brian Daniels, M.D. Senior Vice President, Head Global Development &
Medical Affairs
Fred Fiedorek, M.D. Senior Vice President, Head of CV and Metabolic
Development
James List, M.D., Ph.D. Vice President, Development Lead Dapagliflozin
Agata Ptaszynska, M.D. Group Director, Global Clinical Research-
Metabolics
David Henry, Ph.D. Executive Director, Global Biometric Sciences
Cardiovascular and Metabolics

AstraZeneca

Peter Honig, M.D., M.P.H. VP, Global Regulatory Affairs
Howard G. Hutchinson, M.D., FACC Chief Medical Officer AZ
Jonathan Fox, M.D. Vice President, CV/GI Clinical Development,
Elisabeth Björk, M.D., Ph.D. Vice President, Development
Shamik Parikh, M.D. Executive Director, Clinical Development CV/GI
(AZ Medical lead)

BACKGROUND

Bristol-Myers Squibb (BMS) submitted NDA 202293 for dapagliflozin tablets, a sodium-glucose transporter-2 (SGLT2) inhibitor, being developed for treatment of type 2 diabetes mellitus, on December 27, 2010. On January 17, 2012, a complete response letter issued for NDA 202293.

The sponsor requested an End-of-Review (EOR) meeting to discuss the deficiencies described in the complete response letter and to discuss actions to address these deficiencies.

DISCUSSION

The sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the sponsor on April 27, 2012, follow in bold font. A revision to the preliminary response is noted in italicized bold font. A summary of the meeting discussion is indicated in italicized font.

Question 1

a. Considering the current dapagliflozin profile and the expectations for Sponsors agreed in the 2008 FDA Guidance [Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes], BMS/AZ do not consider that confirmed CV [cardiovascular] benefit should be required for approval of dapagliflozin. Does the Agency agree?

FDA Preliminary Response: The December 2008 Guidance for Industry outlining the expectations for evaluating cardiovascular (CV) risk of new anti-diabetic therapies does not require demonstration of CV benefit. However, should a new anti-diabetic therapy carry a serious safety concern that sets it apart from other available therapies, a counterbalancing benefit beyond glycemic control may be necessary to justify its approval.

Meeting Discussion: None

b. As described in Section 4.3.4.4 [of the meeting background package], we consider it more appropriate to look at MACE [major adverse cardiovascular events] for all patients at high CV risk across the program and not just those from studies D1690C00018 [entitled “A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28 week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care”] and D1690C00019 [entitled “A 24-week multicentre, randomized, double-blind, age stratified, placebo-controlled Phase III study with a 28- week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycaemic control on usual care”]. Does the Agency agree? If not, can the Agency explain their rationale?

FDA Preliminary Response: The two studies you refer to - D1690C00018 and D1690C00019 - were designed to look at the glycemic endpoint as well as the composite endpoint (including blood pressure (BP), weight loss and HbA1c). They were also designed to capture additional information on cardiovascular risks in the event that your original meta-analysis to assess CV risk failed to exclude 1.8.

As such, these two studies enrolled patients with high baseline CV risks, as evidenced by the higher event rates than the other clinical trials in your metaanalysis. Studies 18 and 19 were also able to capture a sizeable number of CV events relative to the overall meta-analysis (~ 40%) despite a 6-month mean duration of treatment. Although the Guidance for Industry does not require that each individual study or subgroup of studies excludes 1.8, a review of a metaanalysis of multiple clinical trials does require subgroup analyses, including that of relevant trials that yield a high number of CV events, to demonstrate internal consistency to the overall findings.

As stated above, Studies 18 and 19 were relevant studies because of the patient population enrolled and the number of events they contributed to the overall meta-analysis. Furthermore, they were sufficiently similar in design to be pooled *in analyses that retain the randomization within a study (i.e. pooled analyses of the two studies is stratified by study)*.

Their separate analyses revealed inconsistent results to the overall meta-analysis with hazard ratios exceeding 1.0 for both the primary composite endpoint and MACE endpoints.

We do not agree with your approach to combine the CV results from Studies 18 and 19 with an analysis of a subset of patients from the remaining 17 Phase 2/3 clinical trials who meet eligibility criteria for Studies 18 and 19. This type of analysis may dilute out a signal of concern from two well-designed, prospective trials through the addition of retrospectively identified high CV risk patients from 17 disparate clinical trials.

Meeting Discussion: The Agency commented on the appropriateness of including a subpopulation from 17 studies with two full studies (Studies 18 and 19) into a meta-analysis. It was expressed that inclusion of two studies from similar patient populations with the remaining 17 studies for which there was a known favorable CV signals may washout any real observed signals, especially in a high CV risk patient population. In addition, the Agency expressed concerns that signals observed in Studies 18 and 19 may be more meaningful than those observed in the 17 other trials as these are longer in duration.

The sponsor stated that an analysis of high CV risk patients (this included Studies 18 and 19 plus a subgroup of patients from the other 17 studies) was pre-specified and the data submitted from Studies 18 and 19 had similar exposure as those from the other 17 other trials as Studies 18 and 19 are still ongoing.

The sponsor stated that Studies 18 and 19 were not designed to find reduction in CV risk. They showed on their slide titled "Probability of MACE in Studies 18/19" how four events early on in the studies had caused the lines for % patients with events over time to separate early on in the

trials. This separation remained consistent throughout the treatment period. The Agency inquired why at 52 weeks of treatment in Studies 18 and 19 is a cardiovascular benefit still not being seen. The company responded that the trials were not powered or designed to show reduction of CV events.

Whether or not the studies were powered to fully characterize CV risk, the Agency must make an assessment with what data are submitted. Regardless of any pre-specification, the Agency maintains that both Studies 18 and 19 are adequate and well-designed trials in a relevant population and when asked, BMS/AZ did not dispute that point. And based on the Agency's view of these two trials, it is difficult to dismiss the discordant findings from these trials relative to the other 17 trials.

c. BMS/AZ consider that clinically relevant BP [blood pressure] reductions observed across the diabetes NDA studies and being quantified further in 2 ongoing dedicated BP studies (MB102073 [entitled "A multicenter, randomized, double-blind, placebocontrolled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in subjects with type 2 diabetes with inadequately controlled hypertension on and angiotensin-converting enzyme inhibitor (ACEI) or angiotension receptor blocker (ARB)"] and MB102077 [entitled "A multicenter, randomized, double-blind, placebocontrolled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in subjects with type 2 diabetes with inadequately controlled hypertension treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and an additional antihypertensive medication"]) would indicate a unique benefit to patients with T2DM [type 2 diabetes mellitus]. Considering that BP reduction is accepted as lowering the risk of CV morbidity and mortality, these data would enhance the benefit-risk assessment for dapagliflozin and support approvability of the dapagliflozin NDA. Does the Agency agree?

FDA Preliminary Response: Favorable BP results from a well-designed study to assess BP outcomes may enhance the benefit-risk assessment. However, a reduction in BP is with the intent of improving CV risk, as stated in your question.

Studies 18 and 19 were designed to also evaluate the BP-lowering effect of dapagliflozin in its composite endpoint yet the clinical CV events (MACE) are numerically higher in dapagliflozin-treated patients. It remains problematic that while you may demonstrate a reduction in blood pressure, there is not a parallel finding of reduced CV event rates with dapagliflozin in those two trials.

Meeting Discussion: At the meeting, BMS/AZ stated that these trials are 12 weeks in duration. The Agency does not believe that 12-weeks trials to assess the effect of dapagliflozin on blood pressure reduction will contribute significantly to a benefit assessment if imbalances in CV risks not favoring dapagliflozin remain.

Question 2

Does the Agency agree [with BMS/AZ's planned approach to characterize the potential bladder cancer and liver toxicity risks, and that the response to the complete response letter should focus on further establishing potential benefit while accruing additional safety experience]? If not, can the Agency provide guidance on what additional measures will be needed to characterize these potential risks pre-marketing to support potential approval of dapagliflozin?

FDA Preliminary Response: You should characterize the potential bladder cancer and liver toxicity risks by accumulating additional clinical trial follow-up data.

On page 45 of your submission, you mentioned that you plan to conduct postmarketing pharmacoepidemiology studies on acute liver injury, acute kidney injury, severe complications of urinary tract infections, and cancer. Please review the FDA recommendations sent on August 6, September 29 and December 7, 2011, concerning the pharmacoepidemiology studies for which you submitted preliminary proposals.

Meeting Discussion:

Discussion on liver toxicity:

The sponsor discussed the possible drug induced liver injury (DILI) case and explained that the patient had removed consent from the trial. However, in their recent follow up of this patient, he is on immunosuppressive medications and is being treated as if he has autoimmune hepatitis. There have been no other DILI cases and transaminase shifts were not seen. The sponsor expressed that they are not sure how to proceed with respect to liver toxicity risk. The Agency advised the sponsor that when there is a single concerning case of possible DILI, more controlled clinical trial data are typically necessary to provide reassurance that the finding is spurious or if the risk is present, it is diminishingly low.

Discussion on bladder cancer and tumor promotion:

The Agency asked if nonclinical studies were conducted that addressed the tumor promotion potential of dapagliflozin, such as experiments with various malignant cell lines. The sponsor noted that studies were recently done with several bladder cancer cell lines exposed to various glucose concentrations, and further cited the existing nonclinical data that evaluated the tumorigenic potential of dapagliflozin. The Agency suggested that an in vivo model of bladder tumor initiation/promotion (e.g., BBN induction) would be the preferred approach, and that such data could contribute to a weight-of-evidence argument regarding the tumor promoting potential of dapagliflozin. The sponsor noted that nonclinical experts from the Committee for Medicinal Products for Human Use (CHMP) discussed this issue, and would be willing to share notes from that discussion with the Agency.

Question 3

Does the agency agree with this resubmission proposal [presented in Section 4.4 of the meeting background package]? If not, what additional trial data from ongoing and/or to be initiated clinical studies does the Agency require?

FDA Preliminary Response: Our January 17, 2012, Complete Response letter identified three clinical safety concerns associated with dapagliflozin: bladder cancer; liver safety; and discordant CV safety findings in Studies 18 and 19 from the overall Phase 2 and 3 clinical trials. To address these concerns, we requested additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, we required the 52-week data from Studies 18 and 19 because it was noted that the earlier meta-analysis of these two trials was from a mean duration of 6-months of exposure.

In your background package for this End-of-Review meeting you stated that there were 9 CV MACE events identified in Studies 18 and 19 from 52-week data. We requested details of these cases and in your response received on April 25, 2012, you identified 5 of the MACE events to be in the dapagliflozin group versus 4 in control.

Preliminary calculations of CV risk estimates based on this updated information do not alter the original CV analysis of these two trials. Therefore, it remains concerning that even after one year of exposure to dapagliflozin in Studies 18 and 19, there remains an unfavorable CV assessment in a high risk patient population.

We also requested that you provide us with an updated risk estimate for bladder cancer given the additional patient-years of exposure. As no additional cases were observed in either dapagliflozin or comparator groups, your risk estimates have not changed appreciably from your original NDA submission and there remains a calculated incidence rate ratio that exceeds 5.0.

Overall, your proposed plan for resubmission does not appear to provide us with sufficient data to address the safety concerns in your NDA. We propose that the discussion at your End-of-Review meeting on April 30, 2012, focus on what additional data you have remaining in your ongoing clinical development, including your plans to initiate your cardiovascular outcomes trial.

Meeting Discussion:

Please see the response for Question 2 for some discussion on liver toxicity and bladder cancer risks. For CV safety, the sponsor informed the Agency that there had been a 60% drop out for the extension of these two studies because these trials were not designed as CV outcomes trials hence it is not clear if their 2-year completion will provide further clarity on CV risk assessment if the Agency focuses only on these two trials.

Regarding the inadequacy of Studies 18 and 19, the Agency asked BMS/AZ if the 2-year data showed a favorable point estimate, would they still be of the mindset that it is an inadequate

trial? The point to be made here is that they must submit the 2-year data for both these studies and we do not believe the 1-year data is adequate for a resubmission to the complete response action letter. Furthermore, completion of Studies 18 and 19 and any additional clinical trial data for which there are no new cases of bladder cancer or liver injury may be reassuring. The Agency stated that if it is willing to look at Studies 18 and 19 in isolation for CV events, the sponsor may be able to make an argument that should also be done for bladder cancer events. They would have to make the case that there was enough exposure in Studies 18 and 19 to expect to see some events in subjects treated with dapagliflozin, based on the rate from the original meta-analysis. This would include an argument regarding how confident the data from Studies 18 and 19 are in disputing what was demonstrated in the original meta analysis.

The Agency repeated that full two year data from Studies 18 and 19 may be a possible avenue for resubmission.

The sponsor questioned if they should indeed plan to conduct their dedicated CV trial. They also mentioned that patients with hematuria were being excluded from the study.

The Agency responded that they should plan to conduct their CV trial. This was conveyed to BMS/AZ even before the advisory committee that FDA would expect the conduct of a CV outcomes trial. The Agency also requested an updated and more detailed Statistical Analysis Plan (SAP) for the CV protocol currently in house. The Agency commented that the sponsor should consider not excluding hematuria from the dedicated study. This may dilute the ability to obtain an appropriate bladder cancer signal.

The sponsor stated that they will likely request another meeting to discuss steps to address the complete response action.

Additional Comments:

If the drop out rate for Studies 18 and 19 proves to impede resubmission, the sponsor should consider evaluating data from their dedicated CV trial in an interim analysis. At this time, they could formally assess CV risk along with reevaluating the risk for bladder cancer, liver toxicity and transaminase shifts. The sponsor should refer to the Agency's comments on the proposed protocol for the CV outcomes trial, issued in a separate correspondence.

ATTACHMENTS AND HANDOUTS

Slides presented by the sponsor at the meeting

19 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MEHREEN HAI
05/30/2012



NDA 202293

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - U.S.
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to your correspondence dated January 19, 2012, requesting an End-of-Review meeting.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Monday, April 30, 2012, from 2:30 – 3:30 p.m. with the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

Your questions are repeated below, followed by our preliminary responses in **bold** print:

Question 1

- a. Considering the current dapagliflozin profile and the expectations for Sponsors agreed in the 2008 FDA Guidance [Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes], BMS/AZ do not consider that confirmed CV [cardiovascular] benefit should be required for approval of dapagliflozin. Does the Agency agree?

FDA Preliminary Response: The December 2008 Guidance for Industry outlining the expectations for evaluating cardiovascular (CV) risk of new anti-diabetic therapies does not require demonstration of CV benefit. However, should a new anti-diabetic therapy carry a serious safety concern that sets it apart from other available therapies, a counterbalancing benefit beyond glycemic control may be necessary to justify its approval.

- b. As described in Section 4.3.4.4 [of the meeting background package], we consider it more appropriate to look at MACE [major adverse cardiovascular events] for all patients at high CV risk across the program and not just those from studies D1690C00018 [entitled “A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28 week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care”] and D1690C00019 [entitled “A 24-week multicentre, randomized, double-blind, age stratified, placebo-controlled Phase III study with a 28-week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes and cardiovascular disease, who exhibit inadequate glycaemic control on usual care”]. Does the Agency agree? If not, can the Agency explain their rationale?

FDA Preliminary Response: The two studies you refer to - D1690C00018 and D1690C00019 - were designed to look at the glycemic endpoint as well as the composite endpoint (including blood pressure (BP), weight loss and HbA1c). They were also designed to capture additional information on cardiovascular risks in the event that your original meta-analysis to assess CV risk failed to exclude 1.8. As such, these two studies enrolled patients with high baseline CV risks, as evidenced by the higher event rates than the other clinical trials in your meta-analysis. Studies 18 and 19 were also able to capture a sizeable number of CV events relative to the overall meta-analysis (~ 40%) despite a 6-month mean duration of treatment. Although the Guidance for Industry does not require that each individual study or subgroup of studies excludes 1.8, a review of a meta-analysis of multiple clinical trials does require subgroup analyses, including that of relevant trials that yield a high number of CV events, to demonstrate internal consistency to the overall findings.

As stated above, Studies 18 and 19 were relevant studies because of the patient population enrolled and the number of events they contributed to the overall meta-analysis. Furthermore, they were sufficiently similar in design to be pooled. Their separate analyses revealed inconsistent results to the overall meta-analysis with hazard ratios exceeding 1.0 for both the primary composite endpoint and MACE endpoints.

We do not agree with your approach to combine the CV results from Studies 18 and 19 with an analysis of a subset of patients from the remaining 17 Phase 2/3 clinical trials who meet eligibility criteria for Studies 18 and 19. This type of analysis may dilute out a signal of concern from two well-designed, prospective trials through the addition of retrospectively identified high CV risk patients from 17 disparate clinical trials.

- c. BMS/AZ consider that clinically relevant BP [blood pressure] reductions observed across the diabetes NDA studies and being quantified further in 2 ongoing dedicated BP studies (MB102073 [entitled “A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in subjects with type 2 diabetes with inadequately controlled hypertension on and angiotensin-converting enzyme inhibitor (ACEI) or angiotension receptor blocker (ARB)”] and MB102077 [entitled “A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in subjects with type 2 diabetes with inadequately controlled hypertension treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and an additional antihypertensive medication”]) would indicate a unique benefit to patients with T2DM [type 2 diabetes mellitus]. Considering that BP reduction is accepted as lowering the risk of CV morbidity and mortality, these data would enhance the benefit-risk assessment for dapagliflozin and support approvability of the dapagliflozin NDA. Does the Agency agree?

FDA Preliminary Response: Favorable BP results from a well-designed study to assess BP outcomes may enhance the benefit-risk assessment. However, a reduction in BP is with the intent of improving CV risk, as stated in your question. Studies 18 and 19 were designed to also evaluate the BP-lowering effect of dapagliflozin in its composite endpoint yet the clinical CV events (MACE) are numerically higher in dapagliflozin-treated patients. It remains problematic that while you may demonstrate a reduction in blood pressure, there is not a parallel finding of reduced CV event rates with dapagliflozin in those two trials.

Question 2

Does the Agency agree [with BMS/AZ’s planned approach to characterize the potential bladder cancer and liver toxicity risks, and that the response to the complete response letter should focus on further establishing potential benefit while accruing additional safety experience]? If not, can the Agency provide guidance on what additional measures will be needed to characterize these potential risks pre-marketing to support potential approval of dapagliflozin?

FDA Preliminary Response: You should characterize the potential bladder cancer and liver toxicity risks by accumulating additional clinical trial follow-up data.

On page 45 of your submission, you mentioned that you plan to conduct postmarketing pharmacoepidemiology studies on acute liver injury, acute kidney injury, severe complications of urinary tract infections, and cancer. Please review the FDA recommendations sent on August 6, September 29 and December 7, 2011, concerning the pharmacoepidemiology studies for which you submitted preliminary proposals.

Question 3

Does the agency agree with this resubmission proposal [presented in Section 4.4 of the meeting background package]? If not, what additional trial data from ongoing and/or to be initiated clinical studies does the Agency require?

FDA Preliminary Response: Our January 17, 2012, Complete Response letter identified three clinical safety concerns associated with dapagliflozin: bladder cancer; liver safety; and discordant CV safety findings in Studies 18 and 19 from the overall Phase 2 and 3 clinical trials. To address these concerns, we requested additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, we required the 52-week data from Studies 18 and 19 because it was noted that the earlier meta-analysis of these two trials was from a mean duration of 6-months of exposure.

In your background package for this End-of-Review meeting you stated that there were 9 CV MACE events identified in Studies 18 and 19 from 52-week data. We requested details of these cases and in your response received on April 25, 2012, you identified 5 of the MACE events to be in the dapagliflozin group versus 4 in control. Preliminary calculations of CV risk estimates based on this updated information do not alter the original CV analysis of these two trials. Therefore, it remains concerning that even after one year of exposure to dapagliflozin in Studies 18 and 19, there remains an unfavorable CV assessment in a high risk patient population.

We also requested that you provide us with an updated risk estimate for bladder cancer given the additional patient-years of exposure. As no additional cases were observed in either dapagliflozin or comparator groups, your risk estimates have not changed appreciably from your original NDA submission and there remains a calculated incidence rate ratio that exceeds 5.0.

Overall, your proposed plan for resubmission does not appear to provide us with sufficient data to address the safety concerns in your NDA. We propose that the discussion at your End-of-Review meeting on April 30, 2012, focus on what additional data you have remaining in your ongoing clinical development, including your plans to initiate your cardiovascular outcomes trial.

Please provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call me, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEHREEN HAI
04/27/2012



Jonathan B. Zung, Ph.D.
Vice President of Global Development Operations
Bristol-Myers Squibb
PO Box 4000
Princeton, NJ 08543

Dear Dr. Zung:

Between July 19 and 27, 2011, Ms. Dawn Wynder and Ms. Denise Visco, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct as the sponsor of the following clinical investigations of the investigational drug dapagliflozin:

- 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."

We are aware that at the conclusion of the inspection, Ms. Wynder and Ms. Visco presented and discussed with you Form FDA 483, Inspectional Observations.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report, the documents submitted with that report, and your August 10, 2011 written response to the Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

You did not ensure that the investigations were conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50].

Protocol MB102013 and Protocol MB102014 specified that orthostatic vital signs (blood pressures and heart rates) were to be measured after the seated blood pressure and heart rate on visits Day 1, Week 1, Week 12 and Week 24. Protocol MB102030 specified that orthostatic vital signs (blood pressures and heart rates) were to be measured after the seated blood pressure and heart rate on visits Day 1, Week 1, and Week 24. The orthostatic vital signs were to be measured by measuring the supine vital signs first followed by the standing vital signs. Specifically, for five of the nine clinical site monitoring records reviewed, it was noted that the sites were not conducting the orthostatic vital signs according to the protocol and were not re-educated by the monitors.

We acknowledge that you appear to have taken appropriate corrective action to prevent the recurrence of the findings above.

We appreciate the cooperation shown to Investigators Wynder and Visco during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5246
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

TEJASHRI S PUROHIT-SHETH
03/22/2012



NDA 202293

MEETING REQUEST GRANTED

Bristol-Myers Squibb Company
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to your correspondence dated February 7, 2012, requesting a Type C meeting to have a high-level discussion on the benefit/risk required for diabetes drugs as well as how the Agency views the need for new classes of drugs versus the known benefits/risks of existing drug classes. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: Monday, April 30, 2012
Time: 1:30 – 2:30 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

CDER participants (tentative):

Office of New Drugs

Janet Woodcock, M.D.	Director, Center for Drug Evaluation and Research
John Jenkins, M.D.	Director, Office of New Drugs
Robert Temple, M.D.	Deputy Center Director for Clinical Science
Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Lina Aljuburi, M.S., Pharm.D.	Chief, Project Management Staff, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mehreen Hai: x65073; Lena Staunton: x67522.

Submit background information for the meeting (one electronic copy to the application and 8 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **March 30, 2012**, we may cancel or reschedule the meeting.

Submit the 8 desk copies to the following address:

Mehreen Hai
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3391
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEHREEN HAI
02/09/2012



NDA 202293

MEETING REQUEST GRANTED

Bristol-Myers Squibb Company
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets.

We also refer to your correspondence dated January 19, 2012, requesting an End-of-Review meeting to discuss the deficiencies described in our Complete Response letter dated January 17, 2012, and to discuss actions to be taken to address these deficiencies. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: Monday, April 30, 2012
Time: 2:30 – 3:30 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

CDER participants (tentative):

Office of New Drugs

John Jenkins, M.D.	Director, Office of New Drugs
Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Jean-Marc Guettier, M.D.	Acting Diabetes Clinical Team Leader, DMEP
Somya Dunn, M.D.	Clinical Reviewer, DMEP
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Jonathan Norton, Ph.D.	Biostatistics Reviewer, Division of Biometrics II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Anita Abraham, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII

Todd Bourcier, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
Mukesh Summan, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP
Amy Egan, M.D., M.P.H.	Deputy Director for Safety, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Julie Marchick, M.P.H.	Acting Chief, Project Management Staff, DMEP

Office of Surveillance and Epidemiology

Diane Wysowski, Ph.D. M.P.H.,	Team Leader, Division of Epidemiology 1 (DEPI)
Julia Ju, Pharm.D., Ph.D.	Pharmacoepidemiologist, DEPI
Christian Hampp, Ph.D.	Pharmacoepidemiologist, DEPI
Margarita Tossa, M.S.	Safety Regulatory Project Manager

Please e-mail me any updates to your attendees at mehreen.hai@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mehreen Hai: x65073; Lena Staunton: x67522.

Submit background information for the meeting (one electronic copy to the application and 25 desk copies to me) at least four weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by **March 30, 2012**, we may cancel or reschedule the meeting.

Submit the 25 desk copies to the following address:

Mehreen Hai
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3391
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
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DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MEHREEN HAI
01/26/2012

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: RE: Dapa- catch up
Date: Wednesday, January 04, 2012 12:35:00 PM

Hi Amy,

Yes, please go ahead and submit these documents to the NDA.

Regarding the labeling, we are currently still working on some internal reviews, so we won't be able to get the labeling back to you by our original estimate of the end of this week.

We also have the following information request:

For the following 5 bladder cancer cases (Day of diagnosis), were these cases detected during long-term, controlled extension periods or were any of these cases detected in uncontrolled extensions?

D1690C00006-1004-6 - D393

D1690C00006-1501-6 - D399

MB102014-34-524 – D512

D160C00006-2206-14 - D581

D1690C00004-4916-2 - D727

Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]

Sent: Tuesday, January 03, 2012 12:57 PM

To: Hai, Mehreen

Cc: Jennings, Amy

Subject: RE: Dapa- catch up

Hi Mehreen,

I hope you had a nice break during the holidays. I am just catching up on a few things and wanted to check to see if you want the following submitted to the dapa NDA:

- Errata to -018 and -019 CSRs. The errata do not change any conclusions from the data. These will be submitted to the IND, but do you also want them submitted to the NDA since the CSRs were submitted to the NDA (more for record keeping)
- Addenda to the -012 CSR to include the narratives and bone mineral density data that we already provided to you as part of a response document over the summer. Since you

already have all of this information, this would just be for record keeping so this information would track with the CSR (currently it is in a response document)

Also, are you still planning to provide further label comments by the end of this week? Will this also include comments on the medication guide? If possible, can you keep me posted on your timeline so I can plan internal meetings accordingly.

Thanks and Happy New Year,
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Tuesday, December 20, 2011 2:36 PM
To: Jennings, Amy
Subject: RE: Labeling comments for dapagliflozin-

Thanks, Amy.

Yes, we will get back to you with our comments probably close to January 6 or so.

Have a wonderful holiday, and hope you get some rest too!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
01/04/2012

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: RE: Labeling comments for dapagliflozin- cartons and container labels
Date: Monday, December 19, 2011 12:15:00 PM
Attachments: [image001.png](#)
[image002.png](#)

Hi Amy,

The presentation below of the (b) (4) 5 mg dose and (b) (4) for the 10 mg dose for the blister packs are acceptable.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Thursday, December 15, 2011 3:38 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Labeling comments for dapagliflozin- cartons and container labels

Hi Mehreen,

As relates to the carton and container label comments: We agree to the changes as proposed by the Agency except for "revising 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) (b) (4))". (b) (4)

(b) (4)

(b) (4)

(b) (4)

We propose to utilize black ink on white foil background for both the 5 mg and 10 mg dapagliflozin doses per our current specifications as we think that this option provides the most contrast between the text and background to facilitate both human readability and bar code readability. To differentiate dose strengths, we propose (b) (4) the 5 mg dose and (b) (4) for the 10 mg dose (see screenshots below for example). Will this be acceptable?



Thanks,
Amy

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/s/

MEHREEN HAI
12/19/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: RE: Labeling comments for dapagliflozin
Date: Wednesday, December 14, 2011 12:32:00 PM
Attachments: [Dapa CC labels.pdf](#)

Hi Amy,

No, there will not be separate comments from OSE on either the PI or the PMRs - their comments have already been incorporated into what we sent you, and that's how it will be for future rounds of labeling too - everyone's comments are incorporated into the single PI document. However, for the Medication Guide, we will send you comments separately, after the Patient Labeling team has finished reviewing it. As for the carton and container labels, comments on those are also sent separately, and that review was just completed, so I'm attaching those comments.

Hope that makes sense?

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Tuesday, December 13, 2011 8:49 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Labeling comments for dapagliflozin

Hi Mehreen,

We are working towards providing a response by the middle of next week. I should have a more clear picture of the timeline by Friday. Is this target acceptable? Also, just so I understand process etc., has OSE already reviewed/provided comments on the label and PMRs (via this round) or should we expect a separate round of comments from them etc?

Thanks
Amy

From: Hai, Mehreen [<mailto:Mehreen.Hai@fda.hhs.gov>]
Sent: Friday, December 09, 2011 3:42 PM
To: Jennings, Amy
Subject: Labeling comments for dapagliflozin

Hi Amy,
Please find attached our first round of comments and edits to the package insert for dapagliflozin. As

our senior management is occupied in reviewing the application and working towards a regulatory decision, clearance from the Division Director and the Office Director is still pending on these labeling comments. You should expect continued, possibly major changes to the label in the near future. Finally, we remind you that we are sending you these labeling comments according to the 21st Century Review timelines, and that this does not reflect on the final regulatory decision for this application.

Also, comments on the Medication Guide and the carton and container labels for dapagliflozin are still pending - we expect to send those to you in the coming weeks.

Please confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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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 [REDACTED] (b) (4) to ‘(Dapagliflozin)’. The dosage strength of this product is based on the active moiety [REDACTED] (b) (4).
3. Remove [REDACTED] (b) (4) on the label.

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 [REDACTED] (b) (4) and 10 mg [REDACTED] (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 [REDACTED] (b) (4) and 10 mg [REDACTED] (b) (4)).

Carton Labeling

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

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/s/

MEHREEN HAI
12/14/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: Labeling comments for dapagliflozin
Date: Friday, December 09, 2011 3:42:00 PM
Attachments: [Dapagliflozin proposed PI- FDA edits 9December2011.doc](#)

Hi Amy,

Please find attached our first round of comments and edits to the package insert for dapagliflozin. As our senior management is occupied in reviewing the application and working towards a regulatory decision, clearance from the Division Director and the Office Director is still pending on these labeling comments. You should expect continued, possibly major changes to the label in the near future. Finally, we remind you that we are sending you these labeling comments according to the 21st Century Review timelines, and that this does not reflect on the final regulatory decision for this application.

Also, comments on the Medication Guide and the carton and container labels for dapagliflozin are still pending - we expect to send those to you in the coming weeks.

Please confirm receipt of this email, and let me know if you have any questions. Once you've had a chance to review our comments, please let me know when we can expect to receive your response.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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

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/s/

MEHREEN HAI
12/09/2011



NDA 202293

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492-7660

Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences US

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010, received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dapagliflozin Tablets, 5 mg and 10 mg.

We also refer to your September 23, 2011, correspondence, received September 26, 2011, requesting review of your proposed proprietary name, Forxiga. We have completed our review of the proposed proprietary name, Forxiga, and have concluded that it is acceptable.

The proposed proprietary name, Forxiga, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your September 26, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Mehreen Hai at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/08/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: Information request for dapa
Date: Wednesday, December 07, 2011 9:26:00 PM

Hi Amy,
We have the following information request for dapagliflozin:

Please provide the six months and one year exposures to dapagliflozin vs. control at the time of the July 15 cut-off.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
12/07/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: Comments on epi protocols
Date: Wednesday, December 07, 2011 11:54:00 AM

Hi Amy,

Also, please see below our comments on the protocols for the pharmacoepidemiology studies regarding UTIs and kidney injury associated with the use of dapagliflozin, that were submitted to the dapagliflozin NDA on August 26, 2011.

=====

[Redacted] (b) (4)

[Redacted] (b) (4)

=====

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)



=====

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
12/07/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"](#)
Subject: RE: meeting today
Date: Wednesday, December 07, 2011 11:53:00 AM

Hi Amy,
Yes, the highlighted section is correct. However, we do have a few edits to the table you included in your email, see in red below:

PMR	FDA Comments
	(b) (4)
Cardiovascular Outcome Trial (CVOT)	No significant discussion regarding the CVOT study since we discussed this in detail at the 4-Oct-2011 meeting.
Pediatric (2 separate studies with separate milestone dates)	PK/PD study: FDA acknowledged the study is about to start. (Provide separate milestone dates for PREA PK study) Clinical Efficacy /Safety study will be required to assess mono-therapy and add-on to metformin. The draft synopsis BMS/AZ submitted with the NDA (same as EU PIP) appears acceptable but more comments may be forthcoming upon review of the protocol. (Provide separate milestone dates for PREA safety and efficacy study.)

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, December 06, 2011 6:31 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: meeting today

Hi Mehreen,

Thanks for the useful discussion today. I wanted to clarify my understanding on a few points. Below is the summary I captured from the meeting. Can you confirm the yellow highlighted text is correct? Or is the 4 and 6 month times noted below how long it will take FDA to review?

FDA informed BMS/AZ of the Post-Marketing Requirements (PMRs) they are considering for dapagliflozin at this time (see table below). They requested we provide them with milestone dates for final protocol submission, study completion and final report submission for these possible PMRs. The final protocol submission needs to allow time for FDA review. **Considering the stage of the current protocols, FDA stated we should allow 6 month for the CV outcome trial protocol and 4 months for the epidemiology protocols from the time we submit the final draft protocol for FDA review to the time we submit the final protocol to FDA (Milestone Date).**

FDA plans to provide us with a written communication stating these PMRs only if/when dapagliflozin is approved.

PMR	FDA Comments
(b) (4)	

Cardiovascular Outcome Trial (CVOT)	No significant discussion regarding the CVOT study since we discussed this in detail at the 4-Oct-2011 meeting.
Pediatric	PK/PD study: FDA acknowledged the study is about to start. Clinical Efficacy /Safety study will be required to assess mono-therapy and add-on to metformin. The draft synopsis BMS/AZ submitted with the NDA (same as EU PIP) appears acceptable but more comments may be forthcoming upon review of the protocol.

Thanks
Amy

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MEHREEN HAI
12/07/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information request
Date: Friday, December 02, 2011 2:55:11 PM

Hi Amy,

We have the following information request for dapagliflozin:

Of the subjects diagnosed with bladder cancer, provide information on the frequency of unscheduled urinary dipstick prior to the diagnosis of cancer. If there were unscheduled dipsticks for some or all of these patients, provide the reason (e.g., genitourinary discomfort or dysuria, rule out UTI, etc).

Please provide a response by COB Tuesday, December 6, 2011, if possible.

Thank you!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
12/02/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request
Date: Monday, November 28, 2011 8:56:46 AM

Hi Amy,

We have the following information request for dapagliflozin:

Please provide an update on the ongoing portion of Studies 18 and 19, specifically:

- 1. How many patients remain in both these trials and what is the expected pt-yr exposure with completion of both these trials?**
- 2. Are all patients still being followed for CV events and are these events being adjudicated in the same fashion as has been done for the CV meta-analysis?**
- 3. When will the final results of Studies 18 and 19 be available for submission to FDA (i.e., complete datasets, not clinical study reports only)?**

Thanks,

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
11/28/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy"; Mannix, Daniel;](#)
Subject: Information request for dapagliflozin
Date: Thursday, November 17, 2011 12:56:01 PM

Hi Amy and Dan,
We have the following information request for the dapagliflozin NDA:

In your document "2011-08-15-bms-512148-response-us-fda-question-clin-q2-q3.pdf" submitted on October 27, 2011, you state that "[t]he difference in incidence rates of malignant and unspecified tumors was calculated using Cochran-Mantel-Haenszel exposure weights, stratified by study, with CIs based on an exact method." Please provide a description of the methodology of your calculation of point estimates and confidence intervals for rate difference, with sufficient detail to allow replication of your estimates for bladder and breast cancer. Please provide justification for the choice of the statistical method.

Please provide your response by Friday, 11/18/2011.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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/s/

MEHREEN HAI
11/17/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request for dapa
Date: Wednesday, November 09, 2011 9:06:41 PM

Hi Amy,

We have the following information request for dapagliflozin:

For patient ID # D1690C00018-201-8 (submitted in an initial and follow-up safety report to IND 68652, on 9/20/11 and 10/3/11, respectively, and in the hepatic adjudication report addendum submitted to NDA 202293 on 10/27/11), please send the following information if you have it:

1) Past Medical History:

Any previous episodes of jaundice, unexplained fevers, RUQ pain suggestive of biliary tree disease?

Any medical problems other than those of cardiac origin?

Past alcohol history?

2) An explanation for the patient's weight loss; was the patient trying to lose weight?

3) An explanation for the transient increase in the ALT, AP, and serum bilirubin level on 9/19/211 from the previous improving values. Was the patient started back on dapagliflozin or is it likely that he passed a gallstone? Was it associated with a repeat of the RUQ pain, with fever or with leucocytosis?

4) Please explain the discrepancy between the values submitted in the safety report and those in the hepatic adjudication report:

	Date	Safety Report	HAR report
Serum bilirubin	8/26/11	4.3/1.3	4.3/3.6
	8/27/11	5.15/1.0	5.25/4.3
	8/29/11	1.39/0.46	1.39/1.2
	8/31/11	0.9/0.37	0.9/0.8
	9/5/11	N	0.7/0.6
	9/19/11	1.9/0.8	1.9/1.6

5) We note that serum alkaline phosphatase was reported as elevated at a number of these visits. Please inform if alkaline phosphatase was fractionated to determine the origin: bone versus hepatic.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
11/09/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request for dapa
Date: Monday, November 07, 2011 2:46:21 PM

Hi Amy,

We have the following information request for dapagliflozin:

1. For all phase 2b and 3 studies included in the 15-Jul-2011 Integrated Safety Database, which gave rise to the updated bladder and breast cancer incidence rates, please provide subject numbers and total person-time of follow-up after randomization for each of the age brackets in Table 1 (b) (4). The table should separate exposed and control subjects and should also be separated by gender. Please respond by **November 9, 2011**.

2. In addition, please provide separately for each included study the number of patients, total follow-up time, and number of bladder and breast cancer cases by sex and exposure status and by the interaction sex*exposure status. Please respond by **November 10, 2011**.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Table 1: Dapagliflozin data and Calculations for Expected Breast Cancer Cases

Age Group	Dapagliflozin Breast Cancer Cases	Dapagliflozin Female Person-Time	SEER Female Breast Cancer Rates	Expected Breast Cancer in Dapagliflozin Patients
20-24	0	5.6	0.000016	0.0001
25-29	0	14.3	0.000083	0.0012
30-34	0	28.8	0.000259	0.0075
35-39	0	59.6	0.000589	0.0351
40-44	0	126.8	0.001209	0.1533
45-49	0	229.4	0.001861	0.4269
50-54	1	357.7	0.002258	0.8077
55-59	1	463.6	0.002802	1.2990
60-64	4	409.5	0.003489	1.4287
65-69	1	222.7	0.003942	0.8779
70-74	1	153.7	0.004100	0.6302
75-79	1	43.1	0.004337	0.1869
80-84	0	6.9	0.004223	0.0291
85+	0	1.0	0.003392	0.0034
Total	9	2122.7	-	5.9

SEER data 2003-2007, SEER 17 crude incidence rates by age, females, breast cancer. Obtained from SEER*Stat November 22, 2010

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/s/

MEHREEN HAI
11/07/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request for NDA 202293
Date: Friday, November 04, 2011 3:08:18 PM

Hi Amy,

We have the following information request for dapagliflozin:

Please indicate where you have listed ALL the studies that are included in the July 15 data cutoff. The exposure at this cutoff date is used for your liver and cancer update; there is an exposure table included in your liver safety update but there is no list of studies. If there is no listing of all these studies, please submit one as soon as possible.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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/s/

MEHREEN HAI
11/04/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request
Date: Thursday, November 03, 2011 4:22:26 PM

Hi Amy,

We have the following information request for dapagliflozin:

- 1) In your database for study D1690C00019, patient D1690C00019-7803-1 has an AECOD of breast mass. Do you have any additional information on this patient? Please request follow-up information on this patient and submit that as soon as possible.**

- 2) Patient D1690C00019-7833-2 is reported in your updated cancer report submitted 10/27/11 as having breast cancer. However, in your database, the AECOD is breast discharge and AETERM is right nipple discharge. Please clarify the discrepancy.**

Please respond to these requests as soon as is feasible, preferably by early next week for request #2.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
11/03/2011



IND 068652
NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your Investigational New Drug Application (IND) and your New Drug Application (NDA) submitted under section 505(i) and 505(b), respectively, of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to the meeting between representatives of your firm and the FDA on October 4, 2011. The purpose of the meeting was to discuss the design of your proposed cardiovascular outcomes trial and your overall pharmacovigilance plan for dapagliflozin.

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

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance

Meeting Date and Time: October 4, 2011; 3:00 – 4:00 PM
Meeting Location: Building 22, White Oak Campus, Silver Spring, MD

Application Number: IND 068652; NDA 202293
Product Name: Dapagliflozin
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb (in collaboration with Astra-Zeneca)

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Office of New Drugs

Curtis Rosebraugh, M.D.	Director, Office of Drug Evaluation II
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Ilan Irony, M.D.	Diabetes Clinical Team Leader, DMEP
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Anita Abraham, Ph.D.	Biostatistics Reviewer, Division of Biometrics VII
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII
Amy Egan, M.D., M.P.H.	Deputy Director for Safety, DMEP
John Bishai, Ph.D.	Safety Regulatory Project Manager, DMEP
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP
Julie Marchick, M.P.H.	Acting Chief, Project Management Staff, DMEP

Office of Surveillance and Epidemiology

Amarilys Vega, M.D., M.P.H.	Risk Management Analyst, Division of Risk Management
Julia Ju, Pharm.D., Ph.D.	Pharmacoepidemiologist, Division of Epidemiology 1 (DEPI)
Diane Wysowski, Ph.D. M.P.H.,	Team Leader, DEPI 1
Solomon Iyasu, M.D. M.P.H.,	Director, DEPI 1

Quocbao Pham, Pharm.D. BCPS,	Safety Evaluator, Division of Pharmacovigilance I (DPV I)
Lanh Green, Pharm.D. M.P.H.,	Safety Evaluator Team Leader, DPV I
Margarita Tossa, M.S.	Safety Regulatory Project Manager

SPONSOR ATTENDEES

Bristol-Myers Squibb

Amy Jennings, PhD, Director, Global Regulatory Sciences-US
Joe Lamendola, PhD, Vice President, US Regulatory Head
Fred Fiedorek, MD, Vice President, VP, Head of CV and Metabolic Development.
James List, MD, PhD, Executive Director, Global Clinical Research -CV/Metabolics
Lisa Ying, PhD, Associate Director, Global Biometric Sciences
Dominic Labriola, PhD, Vice President, Global Biometric Sciences
Jennifer Wood-Ives, PhD, Director-Pharmacoepidemiology, Global Pharmacovigilance and Epidemiology
Andres Gomez, PhD, MPH, Executive Director - Head of Epidemiology, Global Pharmacovigilance & Epidemiology
Douglas Fleming, MD, Director, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology
Roland Chen, MD, Vice President, Medical Safety Assessment, Global Pharmacovigilance and Epidemiology
Shoba Ravichandran, MD, Director, US Medical Affairs

AstraZeneca

Mike Angioli, MS, Senior Director, Global Regulatory Affairs
Jonathan Fox, MD, Vice President, CV/GI Clinical Development,
Elisabeth Björk, MD, PhD Vice President, Development
Shamik Parikh, MD, Executive Director, Clinical Development CV/GI
Jennifer Sugg, MS, Principal Statistician
Barry Sickels, Vice President, US Regulatory Affairs
Eileen E. Ming, MPH, ScD, Director and Principal Scientist, Epidemiology

1. BACKGROUND

The New Drug Application (NDA) for dapagliflozin (an SGL2- inhibitor) was received on December 28, 2010, and is currently under review. The requested indication is for the treatment of Type 2 Diabetes Mellitus. On May 5, 2011, DMEP informed BMS via a teleconference that they would be required to conduct a dedicated cardiovascular (CV) trial as a post-marketing requirement for dapagliflozin, if the NDA was approved. On June 3, 2011, BMS submitted a proposal for the design of a CV trial, along with a request for a meeting to discuss the proposal. The meeting request was granted. Another teleconference was held between BMS and DMEP on July 7, 2011, as a partial response to the meeting request, to further discuss the requirement for a CV trial. A meeting was scheduled for September 7, 2011, to discuss the remaining questions in the meeting request. After the Advisory Committee meeting on July 19, 2011, BMS requested that the September 7 meeting be postponed, and that the scope of the meeting be expanded to include the overall pharmacovigilance plan for dapagliflozin. The meeting was rescheduled for October 4, 2011.

2. DISCUSSION

The sponsor requested responses to the following questions. The questions are repeated below and the Division's preliminary responses provided to the sponsor on September 29, 2011, follow in bold. A summary of the meeting discussion is indicated in italicized bold.

CARDIOVASCULAR OUTCOME TRIAL DESIGN

Question 1: Does the Agency concur that the proposed CV outcome trial design will satisfy the post-marketing requirement (if dapagliflozin is approved for marketing) to evaluate the effect of dapagliflozin on CV safety?

FDA Preliminary Response: *The trial design appears to be adequate; however a full protocol for study D1693C00001, entitled *Dapagliflozin Effect on Cardiovascular Event Incidence in Patients with Diabetes Mellitus*, should be submitted to reach agreements on the design and statistical methodology. We have the following general comments based upon the protocol synopsis:*



(b) (4)

(b) (4)

Meeting Discussion:

(b) (4)

Additional meeting discussion: After discussion of FDA responses to the applicant's questions, the applicant provided FDA with an update on a safety report (Manufacturer number 16038556) of a potential drug-induced liver injury, as follows:

The applicant received a safety report regarding a 71 year old male subject from Argentina, participating in Study D1690C00018, entitled "A 24-week, multicentre, randomized, double-blind, age stratified, placebo-controlled phase III study with a 28 week extension period to evaluate the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes, cardiovascular disease and hypertension, who exhibit inadequate glycemic control on usual care", who was hospitalized and had an important medical event of "hepatitis" (the preferred term used by the investigator).

Blinded study drug was started [REDACTED] (b) (6) and was discontinued [REDACTED] (b) (6). The patient complained of nausea, vomiting, and diffuse abdominal pain and was admitted to the coronary unit, due to his past history of coronary artery disease (CAD). Abdominal exam revealed tenderness to superficial and deep palpation, mostly mid epigastric and right upper quadrant. Percussion was tympanic without defense. Initial laboratory findings were: white blood cell (WBC) 7300 cells/cubic millimeter, total bilirubin 1.7 mg/dL, alkaline phosphatase (ALP) 547 IU/L (elevated), alanine aminotransferase (ALT) 150 IU/L, aspartate aminotransferase (AST) 262 IU/L, and lactate dehydrogenase (LDH) 310 IU/L. Electrocardiogram (ECG) showed pacemaker rhythm alternating with patient's own normal sinus rhythm and negative T waves. Abdominal sonogram showed heterogeneous echo signal, no biliary dilatation, no gallstones, but the exam was poor due to bloating and lack of cooperation by the patient. Investigational treatment was stopped. The next day, alkaline phosphatase increased further to 607 IU/L, and total bilirubin was 4.3 mg/dL (but direct only 1.27 mg/dL), and ALT increased to 504 IU/L and AST to 613 IU/L. Hepatitis A and B serologies were negative. Hepatitis C serology was not available. By [REDACTED] (b) (6) bilirubin and AST were normal and ALT was 133 IU/L (< 3XULN), while alkaline phosphatase was elevated at 547 IU/L (normal range: 90- 360 IU/L). By [REDACTED] (b) (6) all liver tests except alkaline phosphatase (577 IU/L) were normal. The tentative diagnosis was toxic hepatitis. Liver tests were normal at baseline. Prior to the episode, the patient had "influenza" for 3 days [REDACTED] (b) (6) in which he took Tylenol 1000 mg/day. On [REDACTED] (b) (6) the blind was broken and the patient had been randomized to dapagliflozin 10 mg once daily.

The applicant's medical comment summarizes this report as follows:

This 71 year old patient was diagnosed with hepatitis approximately 9.5 months after the initiation of blinded study therapy. The combination of clinical features, including acuity in presentation, the nausea, vomiting and fever, right upper quadrant pain and tenderness, elevated alkaline phosphatase and conjugated bilirubin levels, and the rapidity with which ALT, AST and total bilirubin values subsequently decreased from their peak recorded value, would not normally point to drug induced liver injury as the most likely explanation but rather explained by other diagnoses, such as gallstone, ischemic liver injury or local inflammation. Also, the initial AST/ALT ratio of almost 2 is in favor of extrahepatic source or alternatively an ischemic injury. In view of the above findings and pending additional information, the event was considered not likely related to study therapy.

Post-Meeting Comment: After the meeting, on September 20, 21, 26 and 30, 2011, the applicant received further details from the investigator on this case: The symptoms of abdominal pain followed by nausea and vomiting were preceded by alcohol consumption at a family party. In addition, anti-hepatitis C virus (HCV) was reported as negative.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion

4.0 ACTION ITEMS

No action items

5.0 ATTACHMENTS AND HANDOUTS

The sponsor's slides that were presented at the meeting are attached.

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

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/s/

MEHREEN HAI
11/03/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request for dapa
Date: Monday, October 31, 2011 11:00:06 AM

Hi Amy,

We have the following information request for dapagliflozin:

For studies D1690C00018 and D1690C00019, submit the SAS code used to create the analysis data sets and to produce the key tables in the clinical study reports, such as those showing the disposition, demographics, concomitant medication, and the findings for the primary and secondary endpoints. Include all needed SAS macros and formats.

Please submit this information as soon as possible.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
10/31/2011



NDA 202293

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010 and received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

On October 20, 2011, we received your solicited major amendment dated October 20, 2011, to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is **January 28, 2012**.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 9, 2011.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEHREEN HAI
10/26/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa update
Date: Tuesday, October 18, 2011 11:56:17 AM

Hi Amy,

We had some internal discussions in the last couple of days regarding the submissions that you've detailed below. With the major amendment and the anticipated new PDUFA date of January 28, 2012, it is unlikely that we will be able to review the November 30 submissions (study datasets for July datacut, as well as integrated safety datasets used for the analyses) as part of this NDA review. We definitely need to review the November 15 submissions, but the timing is very tight. Is there any way that you can get the November 15 submissions (D1690C00018 and -019 6-month CSRs; narratives for CV events, and updated USPI) to us a week earlier than planned, around November 7 or 8? We're hoping that if you don't need to submit the November 30 submissions, you could maybe re-route the workload towards getting the November 15 submissions to us a week earlier.

Please let me know if this is possible.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Thursday, October 13, 2011 11:18 AM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa update

Hi Mehreen,

Just wanted to update you on some of the planned submissions:

- Submission of a 5 nonclinical reports **(to IND, Friday or next week):**
 - Evaluation of the inhibitory effects of dapagliflozin (BMS-512148) on cytochrome P450 enzymes in human liver microsomes
 - In vitro assessment of the role of renal and hepatic uptake transporters in dapagliflozin (BMS-512148) disposition
 - Evaluation of the UGT1A1 Inhibition Potential by Dapagliflozin (BMS-512148) in Human Liver Microsome Incubations.
 - In vitro Potency of Dapagliflozin (BMS-512148) Against Dog Sodium-Glucose Cotransporters 1 and 2
 - Addendum 02 to the Dapagliflozin Genomic Dossier
- BMS/AZ Minutes from the 4-Oct-2011 meeting w/ response to questions **(emailed yesterday, officially submit to IND and NDA, next week)**

- **D1690C00018 and -019 6 month datasets – trigger major amendment (to NDA no later than Friday 21-Oct-2011 and maybe earlier)**

- **(to NDA by 27-Oct-2011)**
 - Response documents to address liver, bladder cancer, and breast cancer questions including addendum to hepatic adjudication report and hepatic CRFs etc.;
 - CV meta-analysis and CV meta-analysis datasets; and
 - Debarment Certification
- **(to NDA by 3-Nov-2011)**
 - the interim, LT datasets for studies D1690C00018 and D1690C00019 using a datacut of 15-July-2011; and
 - eDISH datasets
- **(to NDA by 15-Nov-2011)**
 - D1690C00018 and -019 6 month CSRs;
 - narratives for CV events; and
 - updated USPI
- **(to NDA by 30-Nov-2011)**
 - Submit the other study datasets for July datacut, as well as integrated safety datasets used for the analyses ; and
 - updated financial disclosures including new studies D1690C00018 and -019

Also, I assume the pediatric PK/PD protocol can be conducted under the current IND. Is this correct?

Thanks
Amy

This message (including any attachments) may contain confidential, proprietary, privileged and/or private information. The information is intended to be for the use of the individual or entity designated above. If you are not the intended recipient of this message, please notify the sender immediately, and delete the message and any attachments. Any disclosure, reproduction, distribution or other use of this message or any attachments by an individual or entity other than the intended recipient is prohibited.

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/s/

MEHREEN HAI
10/18/2011



IND 068652
NDA 202293

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your Investigational New Drug Application (IND) and your New Drug Application (NDA) submitted under section 505(i) and 505(b), respectively, of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to your correspondence dated and received June 3, 2011, requesting a meeting to discuss the design of your proposed cardiovascular outcomes trial, and to your correspondence dated and received July 29, 2011, requesting that the scope of the meeting be expanded to include your overall pharmacovigilance plan.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 4, 2011, from 3:00 – 4:00 PM, at the Food and Drug Administration, White Oak Campus, Silver Spring, Maryland, between Bristol-Myers Squibb and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Preliminary responses to meeting questions

Sponsor's Questions and FDA's Preliminary Responses

Cardiovascular Outcome Trial Design

Question 1: Does the Agency concur that the proposed CV outcome trial design will satisfy the post-marketing requirement (if dapagliflozin is approved for marketing) to evaluate the effect of dapagliflozin on CV safety?

FDA Preliminary Response: The trial design appears to be adequate; however a full protocol for study D1693C00001, entitled *Dapagliflozin Effect on Cardiovascular Event Incidence in Patients with Diabetes Mellitus*, should be submitted to reach agreements on the design and statistical methodology. We have the following general comments based upon the protocol synopsis:

(b) (4)



Question 2: (b) (4)



FDA Preliminary Response: (b) (4)



Question 3:

(b) (4)

FDA Preliminary Response: Yes. Please refer to our comments in response to Question 1.

Risk Management Plan

(b) (4)

Question 4:

(b) (4)

First, we will continue to assess data from ongoing clinical studies.

(b) (4)

Second, we will conduct a large, randomized CV outcomes study that will also enable us to examine the risk of liver injury, cancers overall, breast cancer, and bladder cancer after long-term treatment under controlled conditions. A Data Monitoring Committee (DMC) will provide regular review of safety events throughout the life of the outcomes study, which is planned to continue for 6 years.

Across our clinical studies, both ongoing and new studies, specialized case report forms will be used to further characterize identified cases for liver injury, bladder cancer, and breast cancer. Prospective independent blinded adjudication will take place for events of potential liver injury, potential breast cancer and potential bladder cancer in these studies.

Third, we will evaluate spontaneously reported adverse events. For each case of liver injury, bladder cancer and breast cancer, we will use targeted questionnaires to gather additional information on the clinical characteristics of the event. In addition, as needed, we will have the capability to examine data on adverse events reported spontaneously to FDA's Adverse Event Reporting System (AERS) database.

Fourth, we plan (b) (4) observational pharmacoepidemiology studies

(b) (4)

[Redacted] (b) (4)

Does the Agency agree with the risk management plan [Redacted] (b) (4)
[Redacted]? If not, what suggestions does the Agency have on the
current plans (e.g., comments on trial designs or need for additional evaluation)?

FDA Preliminary Response:

[Redacted] (b) (4) **We agree with the overall plan.**

[Redacted] (b) (4)

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/s/

MEHREEN HAI
09/29/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- questions- re submissions in Oct/Nov
Date: Friday, September 23, 2011 9:34:09 AM

Hi Amy,
In response to your questions below:

- 1) No, we don't need the case report for the one patient under blinded treatment assignment.
- 2) It's fine to provide the financial disclosures by end of November.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Wednesday, September 21, 2011 4:08 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa- questions- re submissions in Oct/Nov

Hi Mehreen,
I have a few f/u questions regarding the submissions we are planning for Oct /Nov:

- Regarding your request, "Liver safety information, including summary data on liver aminotransferases, bilirubin and other relevant tests, enzyme and/or bilirubin elevations exceeding 3X, 5X and 10X the upper limit of normal according to treatment group and dose, reports of all cases referred to the hepatic adjudication committee, and detailed information and case report forms for any potential Hy's Law cases. Submit also the most current report from the Hepatic Adjudication Committee." Do you want case report

forms for potential Hy's law cases if the case comes from a blinded, ongoing study? This may apply to 1 case but I am confirming

- We are planning to provide financial disclosures for -018/-019 studies and to support the data up to the July data-cut. Can we provide this by the end of November?

Thanks
Amy

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MEHREEN HAI
09/26/2011

Hai, Mehreen

From: Greeley, George
Sent: Tuesday, September 20, 2011 4:57 PM
To: Hai, Mehreen
Cc: Addy, Rosemary; Mathis, Lisa; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
Subject: NDA 202-293 Dapagliflozin

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Mehreen,

The email serves as confirmation of the review for Dapagliflozin conducted by the PeRC PREA Subcommittee on September 7, 2011.

The Division presented a partial waiver for patients ages birth through nine years because there are too few children with disease/condition to study and a deferral for patients ^{(b) (4)} to seventeen years of age because additional adult safety or efficacy data is needed for the indication of type II diabetes.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

(b) (4)

The pediatric record is attached for Dapagliflozin.



1_Pediatric_Record
.pdf (61 KB)...

Thanks!

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

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NDA 202293

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - US
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK

09/07/2011

J. Marchick signing for M. Parks



NDA 202293

DEFICIENCIES PRECLUDE DISCUSSION

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010 and received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to our letter dated March 4, 2011, in which we notified you of our target date of September 9, 2011, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals And Procedures – Fiscal Years 2008 Through 2012."

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Julie Marchick
Acting Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK
09/01/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- Info Request- letter to be submitted tomorrow
Date: Tuesday, August 23, 2011 12:51:51 PM

Hi Amy,
Yes, your proposal, as outlined in green below, is acceptable.
In response to your question regarding extension of the PDUFA date, we will issue an extension letter immediately upon receipt of your submission constituting a major amendment, and I will email that letter to you.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Monday, August 22, 2011 5:04 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa- Info Request- letter to be submitted tomorrow

Hi Mehreen,

Thanks for your quick response. Please see some comments below in green.
Please let me know if this is acceptable.

Also, if our proposal is acceptable, how will this be communicated? Will you send us a letter stating the PDUFA date has been moved back 3 months? Or is there some other way this is communicated? I ask because we will be obligated at some point to communicate the delay in PDUFA date externally and want to make sure we handle this appropriately.

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, August 19, 2011 5:49 PM
To: Jennings, Amy
Subject: RE: Dapa- Info Request- letter to be submitted tomorrow

Hi Amy,
Please see our response below to the proposal you emailed me yesterday and that was officially submitted today to the dapagliflozin NDA:

Questions to the Agency:

1. Does our proposal as described in Table 1 satisfy the FDA's 15-Aug-2011 request for additional information?

FDA Response: Yes. However, in response to FDA's request number 1, you proposed to submit 6-month datasets for the ongoing trials 18 and 19 by October 27, 2011. We request that you submit these datasets by October 24, 2011. Regarding your response to our request 5, we request that you make every effort to submit the CV metanalyses by mid-September. **We will submit the 6-month datasets for the ongoing trials 18 and 19 by October 24, 2011. We can submit slides with preliminary CV meta-analyses results for Studies 18/19 as well as for all studies for the primary and secondary endpoints (MACE + Hospitalization for unstable angina/MACE) by mid-September and submit the final CV meta-analysis by 27-Oct-2011. All other timelines will be as provided in the letter emailed 18-Aug-2011. Is this acceptable to the Agency?**

2. Does the Agency want us to submit the Full 6-month CSRs for Studies D1690C00018 and D1690C00019, and/or the datasets for

the 15-July-2011 integrated safety datacut, understanding these documents and datasets would be submitted at the timelines described in the above table which is after the major amendment submission on 27-Oct-2011?

FDA Response: Yes, we would like you to submit the Full 6-Month CSRs for both studies by November 15th (or earlier, if feasible). Please submit the datasets by November 3rd, in the format that meets eDISH data requirements, as you had done in May 2011 after discussion with Ted Guo and others at FDA. Please submit datasets for the other studies listed (MB102-035, D1690C00010 and LT extensions from MB102-029, D1690C0004 and D1690C00012 by November 30. **We will submit these as per the dates on the letter or earlier, if available earlier. We will also submit the edish datasets per your request.**

3. If the Agency agrees with the proposal in Table 1, we would also plan to submit an updated proposed US package insert for FDA's review which will incorporate the new data to be included in the major amendment. We would target to submit this in Nov-2011. Is this acceptable to the Agency?

FDA Response: Yes, this is acceptable.

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Thursday, August 18, 2011 6:48 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: Dapa- Info Request- letter to be submitted tomorrow

Hi Mehreen,

Attached is the letter that will be submitted tomorrow which provides a proposal to satisfy your information request dated 15-Aug-2011. I am happy to walk through the letter with you tomorrow if you think this would be helpful. Also, do you know when you will be able to let us know if our proposal is acceptable?

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Monday, August 15, 2011 1:52 PM
To: Jennings, Amy
Subject: Info Request

Hi Amy,
Please see attached an info request letter for the dapagliflozin NDA, detailing what we discussed in the phone conversation on August 8. The paper copy should come to you in the mail in a few days.

We are also requesting that you let us know by the end of this week, whether or not you think you will be able to submit the requested information before the user fee goal date (October 28). This will help us to plan things at our end.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov

Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/23/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- Info Request- letter to be submitted tomorrow
Date: Friday, August 19, 2011 5:48:56 PM

Hi Amy,
Please see our response below to the proposal you emailed me yesterday and that was officially submitted today to the dapagliflozin NDA:

Questions to the Agency:

1. Does our proposal as described in Table 1 satisfy the FDA's 15-Aug-2011 request for additional information?

FDA Response: Yes. However, in response to FDA's request number 1, you proposed to submit 6-month datasets for the ongoing trials 18 and 19 by October 27, 2011. We request that you submit these datasets by October 24, 2011. Regarding your response to our request 5, we request that you make every effort to submit the CV metanalyses by mid-September.

2. Does the Agency want us to submit the Full 6-month CSRs for Studies D1690C00018 and D1690C00019, and/or the datasets for the 15-July-2011 integrated safety datacut, understanding these documents and datasets would be submitted at the timelines described in the above table which is after the major amendment submission on 27-Oct-2011?

FDA Response: Yes, we would like you to submit the Full 6-Month CSRs for both studies by November 15th (or earlier, if feasible). Please submit the datasets by November 3rd, in the format that meets eDISH data requirements, as you had done in May 2011 after discussion with Ted Guo and others at FDA. Please submit datasets for the other studies listed (MB102-035, D1690C00010 and LT extensions from MB102-029, D1690C0004 and D1690C00012 by November 30.

3. If the Agency agrees with the proposal in Table 1, we would also plan to submit an updated proposed US package insert for FDA's review which will incorporate the new data to be included in the major amendment. We would target to submit this in Nov-2011. Is this acceptable to the Agency?

FDA Response: Yes, this is acceptable.

=====

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Thursday, August 18, 2011 6:48 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: Dapa- Info Request- letter to be submitted tomorrow

Hi Mehreen,

Attached is the letter that will be submitted tomorrow which provides a proposal to satisfy your information request dated 15-Aug-2011. I am happy to walk through the letter with you tomorrow if you think this would be helpful. Also, do you know when you will be able to let us know if our proposal is acceptable?

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Monday, August 15, 2011 1:52 PM
To: Jennings, Amy
Subject: Info Request

Hi Amy,
Please see attached an info request letter for the dapagliflozin NDA, detailing what we discussed in the phone conversation on August 8. The paper copy should

come to you in the mail in a few days.

We are also requesting that you let us know by the end of this week, whether or not you think you will be able to submit the requested information before the user fee goal date (October 28). This will help us to plan things at our end.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/19/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Info Request- f/u
Date: Thursday, August 18, 2011 9:26:09 AM

Hi Amy,
Please see our response to your follow-up question:

Summary statistics for Urine albumin excretion at baseline and at the time of glycemic efficacy endpoint are available from the pooled analysis of the 9-study pool that includes the subgroup of the dedicated moderate renal impairment study with a Baseline eGFR ≥ 45 and < 60 mL/min/1.73m² as well the dedicated moderate renal impairment study. Please confirm, that meets the needs of your request

FDA Response: We agree with the proposed efficacy analyses of the 9-study monotherapy / combination therapy pool overall, as well as its subsets based on categories of renal impairment. But within the subset of moderate renal impairment of the 9-study pool, we would like to see your analysis of all subjects with moderate renal impairment (i.e., those subjects with eGFR between 30 and 60 mL/min/1.73 m²), not only those subjects with eGFR between 45 and 60 mL/min/1.73 m².

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, August 17, 2011 10:52 AM
To: Hai, Mehreen
Cc: Jennings, Amy

Subject: RE: Info Request- f/u

Hi Mehreen,

We have one follow up question (please see below in pink).

Thanks

Amy

From: Jennings, Amy

Sent: Wednesday, August 17, 2011 10:38 AM

To: Hai, Mehreen

Cc: Jennings, Amy

Subject: RE: Info Request

Thanks Mehreen.

Just fyi, by Friday this week we are planning to provide a proposal to address your 15-Aug-2011 letter and also to email the requested pediatric information (w/ formal submission of both next week).

Thanks

Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]

Sent: Tuesday, August 16, 2011 4:56 PM

To: Jennings, Amy

Subject: RE: Info Request

Hi Amy,

Please see our responses below (in bold) to your questions (in green):

As there are no additional bladder cancer cases beyond those already reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (in 6-month datacut), I assume providing you the updated information which will now include exposures from the -018 and -019 trials will satisfy your request for bladder cancer incidence rates. Is this correct?

FDA Response: Correct, but provide incidence rate based on exposure broken down by age categories and gender, similarly to the format provided prior to the AC.

As there are no additional breast cancer cases beyond those already

reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (captured in interim LT July -2011 datacut), I assume providing you the updated information which will now include the exposures from the -018 and -019 trials LT datacut will satisfy your request for breast cancer incidence rates (Note: we have an interim datacut in July-2011 with a database locked planned for sep). Is this correct?

FDA Response: Correct, but provide incidence rate based on exposure broken down by age categories and gender, similarly to the format provided prior to the AC.

We can provide an updated dataset with the same variables and structure as ADCV.XPT. This dataset will contain all Phase 2b and 3 studies, including the new studies: MB102035, D1690C00010, D1690C00018, and D1690C00019. It will also have updated records from long-term extensions of studies that were previously analyzed (e.g. D1690C00004). Additional, relevant variables (e.g. strata variables from D1690C00018 and D1690C00019) will be included. The updated CV meta-analysis will use this dataset, with a cut-off date of July 15, 2011. Raw datasets from D1690C00018 and D1690C00019 are now being prepared for submission to the Agency, as requested (and we will get back to the FDA by the end of this week on when these will be available for submission). At this time, the sponsors are not planning to submit new or updated datasets from other studies. Does the Agency agree?

FDA Response: We agree. Please clarify whether the events included in your individual studies datasets and in the metanalyses have been adjudicated.

We plan to provide FDA the analyses for the changes from baseline at Week 24 (LOCF) in HbA1c by subgroups of normal, micro-, and macroalbuminuria at baseline using the following populations:

- The 9-study Monotherapy /Combination Therapy Pool*
- The subjects with normal renal function from the 9-study Monotherapy /Combination Therapy Pool*
- The subjects with mild renal function from the 9-study Monotherapy /Combination Therapy Pool*

- *Study MB102029 that studied subjects with moderate renal impairment.*

FDA Response: We agree with your plan for analyses of efficacy as a function of the categorical magnitude of renal albumin excretion. Please provide all screening and baseline urine albumin data, and where available, urine albumin excretion (g / g creatinine) at the time of glycemic efficacy endpoint.

Summary statistics for Urine albumin excretion at baseline and at the time of glycemic efficacy endpoint are available from the pooled analysis of the 9-study pool that includes the subgroup of the dedicated moderate renal impairment study with a Baseline eGFR ≥ 45 and < 60 mL/min/1.73m² as well the dedicated moderate renal impairment study. Please confirm, that meets the needs of your request

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/18/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Info Request
Date: Tuesday, August 16, 2011 4:51:17 PM

Hi Amy,

Please see our responses below (in bold) to your questions (in green):

As there are no additional bladder cancer cases beyond those already reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (in 6-month datacut), I assume providing you the updated information which will now include exposures from the -018 and -019 trials will satisfy your request for bladder cancer incidence rates. Is this correct?

FDA Response: Correct, but provide incidence rate based on exposure broken down by age categories and gender, similarly to the format provided prior to the AC.

As there are no additional breast cancer cases beyond those already reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (captured in interim LT July -2011 datacut), I assume providing you the updated information which will now include the exposures from the -018 and -019 trials LT datacut will satisfy your request for breast cancer incidence rates (Note: we have an interim datacut in July-2011 with a database locked planned for sep). Is this correct?

FDA Response: Correct, but provide incidence rate based on exposure broken down by age categories and gender, similarly to the format provided prior to the AC.

We can provide an updated dataset with the same variables and structure as ADCV.XPT. This dataset will contain all Phase 2b and 3 studies, including the new studies: MB102035, D1690C00010, D1690C00018, and D1690C00019. It will also have updated records from long-term extensions of studies that were previously analyzed (e.g. D1690C00004). Additional, relevant variables (e.g. strata variables from D1690C00018 and D1690C00019) will be included. The updated CV meta-analysis will use this dataset, with a cut-off date of July 15, 2011. Raw datasets from D1690C00018 and D1690C00019 are now being prepared for submission to the Agency, as requested (and we will get back to the FDA by the end of this week on when these will be available for submission). At this time, the sponsors are not planning to submit new or updated datasets from other studies. Does the Agency agree?

FDA Response: We agree. Please clarify whether the events included in your individual studies datasets and in the metanalyses have been adjudicated.

We plan to provide FDA the analyses for the changes from baseline at Week 24 (LOCF) in HbA1c by subgroups of normal, micro-, and macroalbuminuria at baseline using the following populations:

- *The 9-study Monotherapy /Combination Therapy Pool*
- *The subjects with normal renal function from the 9-study Monotherapy / Combination Therapy Pool*
- *The subjects with mild renal function from the 9-study Monotherapy / Combination Therapy Pool*
- *Study MB102029 that studied subjects with moderate renal impairment.*

FDA Response: We agree with your plan for analyses of efficacy as a function of the categorical magnitude of renal albumin excretion. Please provide all screening and baseline urine albumin data, and where available, urine albumin excretion (g / g creatinine) at the time of glycemic efficacy endpoint.

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Monday, August 15, 2011 3:57 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Info Request

Hi Mehreen,

Thanks for the letter. It summarizes the points as I understand them from the 8-

Aug-2011 meeting. I have a few questions to your points on the letter as noted below in green:

In order to enable a more accurate assessment of the risks and benefits of dapagliflozin, please provide the 6-month datasets for ongoing clinical trials D1690C000018 and D1690C000019 for review prior to the user fee goal date for this NDA (October 28, 2011). With this amendment, also provide the following:

1. Liver safety information, including summary data on liver aminotransferases, bilirubin and other relevant tests, enzyme and/or bilirubin elevations exceeding 3X, 5X and 10X the upper limit of normal according to treatment group and dose, reports of all cases referred to the hepatic adjudication committee, and detailed information and case report forms for any potential Hy's Law cases. Submit also the most current report from the Hepatic Adjudication Committee.

2. Updated bladder cancer cases and incidence rate, including an analysis of risk factors at screening or baseline, and cases whose diagnosis was preceded by urinary or genital infections prompting increased urine monitoring;

As there are no additional bladder cancer cases beyond those already reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (in 6-month datacut), I assume providing you the updated information which will now include exposures from the -018 and -019 trials will satisfy your request for bladder cancer incidence rates. Is this correct?

3. Updated breast cancer cases and incidence rate, including analysis of risk factors at screening

or baseline, and relevant medical/family history prior to baseline for the cases identified;

As there are no additional breast cancer cases beyond those already reported in the May-2011 neoplasm update and the 3 cases from Studies D1690C000018 and D1690C000019 (captured in interim LT July -2011 datacut), I assume providing you the updated information which will now include the exposures from the -018 and -019 trials LT datacut will satisfy your request for breast cancer incidence rates (Note: we have an interim datacut in July-2011 with a database locked planned for sep). Is this correct?

4. Updated cardiovascular meta-analysis to include MACE reported in these two trials

separately and combined with previously conducted meta-analysis. The data structure should

be similar to ADCV.XPT submitted in the original application.

We can provide an updated dataset with the same variables and structure as ADCV.XPT. This dataset will contain all Phase 2b and 3 studies, including the new studies: MB102035, D1690C00010, D1690C00018, and D1690C00019. It will also have updated records from long-term extensions of studies that were previously analyzed (e.g. D1690C00004). Additional, relevant variables (e.g. strata variables from D1690C00018 and D1690C00019) will be included. The updated CV meta-analysis will use this dataset, with a cut-off date of July 15, 2011. Raw datasets from D1690C00018 and D1690C00019 are now being prepared for submission to the Agency, as requested (and we will get back to the FDA by the end of this week on when these will be available for submission). At this time, the sponsors are not planning to submit new or updated datasets from other studies. Does the Agency agree?

5. In addition to the data above for studies D1690C000018 and D1690C000019, submit any

clinical data from the Phase 2b/ Phase 3 program correlating either categorical status of

proteinuria status (i.e., absent, micro or macroalbuminuria) or actual measures of urinary

protein excretion (mg protein or albumin per gram of creatinine) at baseline

and efficacy
parameters (changes in HbA1c, changes in fasting plasma glucose, etc).

Based on our discussion at the 08•Aug-2011 meeting, we included a proposal to address what we think addresses the FDA's request above in our response to question 7 dated 05-Aug-2011 submitted to the FDA on 12•Aug•2011 (sequence 0039). The proposal is below, Can you let us know if this meets what the FDA is looking for? Note: we did not do FPG in this analyses but can do so if you want them. Please let me know. We are currently planning to submit this response the week of Aug 29.

We plan to provide FDA the analyses for the changes from baseline at Week 24 (LOCF) in HbA1c by subgroups of normal, micro-, and macroalbuminuria at baseline using the following populations:

- *The 9-study Monotherapy /Combination Therapy Pool*
- *The subjects with normal renal function from the 9-study Monotherapy /Combination Therapy Pool*
- *The subjects with mild renal function from the 9-study Monotherapy /Combination Therapy Pool*
- *Study MB102029 that studied subjects with moderate renal impairment.*

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Monday, August 15, 2011 1:52 PM
To: Jennings, Amy
Subject: Info Request

Hi Amy,
Please see attached an info request letter for the dapagliflozin NDA, detailing what we discussed in the phone conversation on August 8. The paper copy should

come to you in the mail in a few days.

We are also requesting that you let us know by the end of this week, whether or not you think you will be able to submit the requested information before the user fee goal date (October 28). This will help us to plan things at our end.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/16/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Dapagliflozin Pediatric Certification and Study Dates
Date: Monday, August 15, 2011 4:19:12 PM

Hi Amy,

Can you please submit an amendment to your pediatric plan to include timelines (M/D/Y) for completion of the studies (this should include the date by when the final protocols will be submitted, the date by when the studies will be completed, and the data by when the complete study reports will be submitted to FDA). When determining a date for final protocol submission, please ensure that there is sufficient time to allow FDA feedback on your draft protocols (the protocol will only be considered final after FDA agrees with the study design).

Please also include certification of the grounds for deferring the studies and evidence that studies will be conducted with due diligence and at the earliest possible time. Let me know if you need me to send you an example of the wording for this.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/15/2011



NDA 202293

INFORMATION REQUEST

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010 and received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

As discussed in the phone conversation on August 8, 2011, between you and Dr. Joseph Lamendola at Bristol-Myers Squibb, and Dr. Mehreen Hai and I at FDA, we have the following information requests.

In order to enable a more accurate assessment of the risks and benefits of dapagliflozin, please provide the 6-month datasets for ongoing clinical trials D1690C000018 and D1690C000019 for review prior to the user fee goal date for this NDA (October 28, 2011). With this amendment, also provide the following:

1. Liver safety information, including summary data on liver aminotransferases, bilirubin and other relevant tests, enzyme and/or bilirubin elevations exceeding 3X, 5X and 10X the upper limit of normal according to treatment group and dose, reports of all cases referred to the hepatic adjudication committee, and detailed information and case report forms for any potential Hy's Law cases. Submit also the most current report from the Hepatic Adjudication Committee.
2. Updated bladder cancer cases and incidence rate, including an analysis of risk factors at screening or baseline, and cases whose diagnosis was preceded by urinary or genital infections prompting increased urine monitoring;
3. Updated breast cancer cases and incidence rate, including analysis of risk factors at screening or baseline, and relevant medical/family history prior to baseline for the cases identified;
4. Updated cardiovascular meta-analysis to include MACE reported in these two trials separately and combined with previously conducted meta-analysis. The data structure should be similar to ADCV.XPT submitted in the original application.

5. In addition to the data above for studies D1690C000018 and D1690C000019, submit any clinical data from the Phase 2b/ Phase 3 program correlating either categorical status of proteinuria status (i.e., absent, micro or macroalbuminuria) or actual measures of urinary protein excretion (mg protein or albumin per gram of creatinine) at baseline and efficacy parameters (changes in HbA1c, changes in fasting plasma glucose, etc).

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
08/15/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- f/u from our call yesterday
Date: Thursday, August 11, 2011 11:11:59 AM

Thanks, Amy.

We're confirmed for Tuesday, October 4, from 3:00 - 4:00 pm, as a face-to-face meeting. Please don't forget to send me the list of attendees and the foreign visitor forms, if any. Also, will you send in desk copies of the meeting material or it is likely to be pretty brief and therefore easily printable from the electronic copy?

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, August 10, 2011 4:31 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa- f/u from our call yesterday

Yes, sorry. Thanks.

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, August 10, 2011 4:30 PM
To: Jennings, Amy
Subject: RE: Dapa- f/u from our call yesterday

Yes, it'll be face-to-face.
So you're ok with the new date and time?

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, August 10, 2011 4:30 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa- f/u from our call yesterday

Thanks Mehreen. Can this still be face-to face? T hanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, August 10, 2011 3:58 PM
To: Jennings, Amy
Subject: RE: Dapa- f/u from our call yesterday

Amy,
We are fine with moving the September 7 meeting to the first week of October.
Does Tuesday, October 4, from 3:00 - 4:00 pm work for you?

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, August 09, 2011 12:16 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa- f/u from our call yesterday

Hi Mehreen,

Just wanted to follow-up on a few things after our meeting yesterday:

- Regarding the scheduled 7-Sep-2011 meeting, we are ok delaying this meeting ~ 1 month but would still like to have this meeting to discuss the design of the CV outcome trial and the epidemiology studies. Is it possible to move this meeting to the 1st week in October? If so, we can target to provide the CV outcome trial synopsis and epidemiology protocols by the 1st week in Sep (with a chance that we may only have a synopsis for the (b) (4) by this point but would have the protocol prior to the meeting)
 - We are still planning to submit the following documents. Can you confirm that these will not trigger a major amendment if submitted to the NDA?
 - A document that provides responses to questions and issues raised at the dapagliflozin EMDAC meeting.
 - A summary of protocol descriptions, scope, and topline results of two recently locked trials in diabetic patients with high CV risk, D1690C000018 and D1690C000019.
 - Pharmacovigilance Plan
 - An updated risk management plan (RMP) (b) (4)
 - Updated package insert (USPI) (b) (4)
 - A Medication Guide which will replace the proposed patient package insert.
 - Updated CV outcome trial synopsis which is also planned to capture bone fracture, liver and cancer safety data.
 - (b) (4)
- We will also include response to your comments (b) (4) submitted with the NDA

- Do you still want us to submit the datasets discussed below? If so, we will be ready to submit them in a week or so. I just want to confirm this will not trigger a major amendment.
- Considering the discussion yesterday, do you still plan to communicate labeling and post market request to us by Sep 9? If not, when should we plan for these?

Thanks,
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, June 15, 2011 3:48 PM
To: Jennings, Amy
Subject: RE: Dapa- Info Request-status update

Hi Amy,
In response to your questions below:

We plan to submit a stand-alone neoplasm summary which will be essentially a cut/paste from the EMDAC briefing document. Should we submit this as an amendment to the NDA or as Other?
Please submit an amendment to the NDA.

Also is it acceptable for us to submit the data to the NDA by mid-August (in the same formats included in the initial NDA e.g. STDM cDISC for raw data and proprietary for analysis).
Yes, this is fine.

Also, in response to your meeting request dated June 2, 2011, to discuss the draft CV trial synopsis, we are going to grant the meeting (official letter to come), but due to scheduling conflicts we can't schedule the meeting until September. However, we want to set up a tcon much sooner than that, with just Dr. Mary Parks and Dr. Curt Rosebraugh, to discuss Question 1, regarding the rationale for the CV outcome trial as a PMR. Would **Thursday, July 7 at 10 am** work for you?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
08/11/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
cc: [Mannix, Daniel;](#)
Subject: Comments [redacted] (b) (4)
Date: Saturday, August 06, 2011 4:33:52 PM

Hi Amy,
Please see below our comments [redacted] (b) (4) that were submitted as part of the Risk Management Plan for the dapagliflozin NDA.

=====

[redacted] (b) (4)

[redacted] (b) (4)

(b) (4)

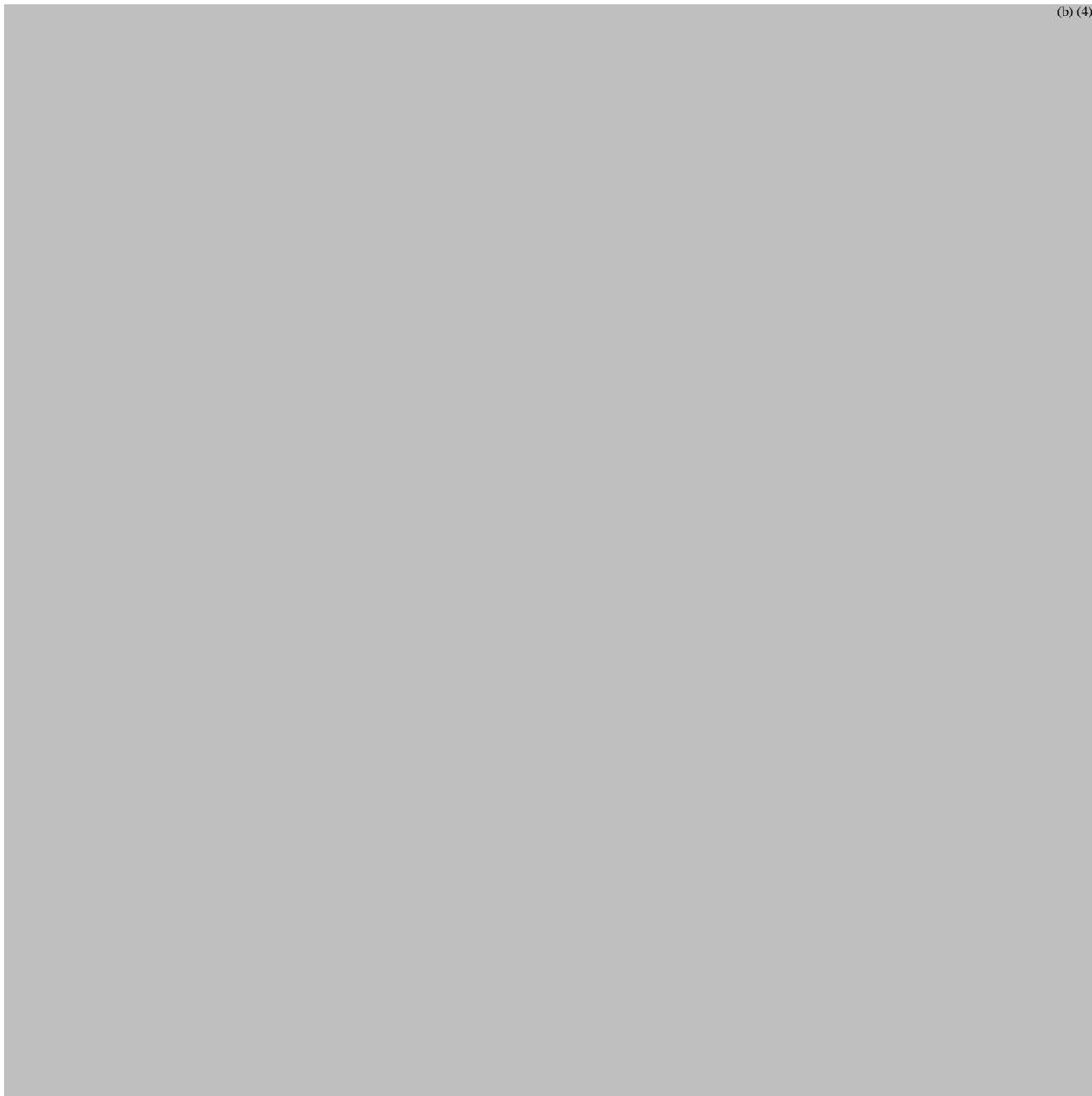


(b) (4)



(b) (4)





=====

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073

Fax: 301-796-9712

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/s/

MEHREEN HAI
08/06/2011

From: [Hai, Mehreen](#)
To: ["june.quattromani@bms.com";](mailto:june.quattromani@bms.com)
cc: [Mannix, Daniel](#); ["Jennings, Amy";](#)
Subject: FW: Information Request for NDA 202293
Date: Friday, August 05, 2011 3:01:27 PM
Attachments: Dapa info request.doc

Hi June,

I understand that you are covering for Dan Mannix, who is in turn covering for Amy Jennings. We have an information request (attached) for NDA 202293 (dapagliflozin), for which we are requesting a response by Tuesday, August 9.

If you could please confirm receipt of this email, I would greatly appreciate it. Thank you,

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Hai, Mehreen
Sent: Friday, August 05, 2011 2:57 PM
To: 'Jennings, Amy'
Cc: Mannix, Daniel
Subject: Information Request

Hi Amy and Dan,
Please see attached an information request for dapagliflozin.
Please respond to these questions by Tuesday, August 9.
Thank you!

Mehreen Hai, Ph.D.

Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

1. At the pre-NDA meeting on November 9, 2010, we requested that you analyze elevations in creatinine phosphokinase greater than 10x ULN as well as cases of rhabdomyolysis as *Adverse Events of Special Interest* in your NDA. These were to have been accompanied by case narratives. Please specify where this analysis is.

2. Please clarify the stratification plan for study D1690C00005.

3. Please clarify where the protocols for the Astra Zeneca studies are located in the NDA submission.

4. In our inquiry to you regarding the baseline renal function in the moderate renal impairment study, MB102029 on May 4, 2011, we asked:

In your renal impairment study MB102029, the inclusion criterion was for patients with moderate renal impairment defined as an eGFR (estimated glomerular filtration rate) value in the range of 30 mL/min/1.73m² to 59 mL/min/1.73m². The description of baseline characteristics for this study population shows that 42.2% of patients randomized to dapagliflozin and 48.8% of patients randomized to placebo had baseline eGFR in the mild insufficiency range (≥ 60 to < 90 mL/min/1.73m²). Please justify why almost half of your patients had mild renal insufficiency.

You responded:

*At enrollment, in accordance with the protocol's entry criterion, all subjects had moderate renal impairment, defined as an eGFR of 30 mL/min/1.73m² to < 60 mL/min/1.73m², and also referred to as Stage 3 chronic kidney disease (CKD). Subsequently, **at baseline** (study Day 1 prior to randomization and initiation of study drug), **91.7% of subjects met this criterion**. This difference is most likely due to variability in serum creatinine concentration, rather than to any specific intervention.*

However, in your table for demographics for study MB102029 submitted in your Response to FDA Inquiry dated 3/31/11, as mentioned above, **48.8% of patients had mild renal insufficiency. Your answer above states that 91.7% of patients had moderate renal insufficiency at baseline.** Please explain the discrepancy.

5. Please direct us to where in the submission you report incidence of micro and/or macroalbuminuria for the phase 2b/3 pool.

6. Please direct us to where in the submission you report macroalbuminuria incidence in study 102029.

7. If you have conducted analyses of changes in HbA1c among subgroups with micro- or macroalbuminuria, please submit these results.

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/s/

MEHREEN HAI
08/05/2011

Executive CAC

Date of Meeting: August 2, 2011

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
John Leighton, Ph.D., OODP, Alternate Member
Todd Bourcier, Ph.D., DMEP, Team Leader
Mukesh Summan, PhD, DABT, DMEP, Presenting Reviewer

Author of Draft: Mukesh Summan and Todd Bourcier

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 202293
Drug Name: Dapagliflozin (b) (4)
Sponsor: Bristol Myers Squibb and Astrazeneca

Background:

Dapagliflozin is a first in class sodium glucose co-transporter 2 (SGLT2) inhibitor. The sponsor is seeking an indication for the treatment of type 2 diabetes mellitus (T2DM).

Mouse Carcinogenicity Study

Carcinogenic assessment in CD-1 mice was initiated at doses of 0 (PEG400 vehicle), 0 (water control), 5, 15, 40 and 120mg/kg for male mice and 0 (PEG400 vehicle), 0 (water control), 2, 10, 20 and 60mg/kg in female mice, respectively. This was in accordance with the Committee's dosing recommendations. The sponsor reduced the clinical dose from 100mg to 20mg so at week 22 of the carcinogenicity study the sponsor requested discontinuation of the high dose in the ongoing carcinogenicity study. The Committee concurred as the mouse to human exposure multiples remained at $\geq 25x$ maximum recommended human dose (MRHD) in the mid dose groups for each gender. The survival rate across the treatment groups was similar to the control groups. Drug exposure at the 5, 15 and 40mg/kg dose groups provided multiples of 4x, 14x, and 72x MRHD in males, respectively, relative to the further revised clinical high dose of 10mg. Drug exposure at the 10, 20 and 60mg/kg dose groups provided multiples of 11x, 52x, and 105x MRHD, respectively, in females relative to the clinical high dose of 10mg.

Rat Carcinogenicity Study

Carcinogenic assessment in Sprague Dawley rats was initiated at doses of 0 (PEG400 vehicle), 0 (water control), 0.5, 2, 10 and 25mg/kg, in accordance with the Committee's dosing recommendations. The sponsor reduced the clinical dose from 100mg to 20mg so at week 25 of the carcinogenicity study the sponsor requested discontinuation of the high

dose in the ongoing carcinogenicity study. The Committee concurred as the rat to human exposure multiples remained at ≥ 25 x maximum recommended human dose (MRHD) in the mid dose groups for each gender. Survival declined significantly in the 0 (vehicle control) and 0 (water control) males at week 87 and consequently all male animals were terminated between weeks 89 to 91. Females were sacrificed at the scheduled termination period. Drug exposure at the 0.5, 2, and 10mg/kg dose groups provided multiples of 7x, 25x, and 130x MRHD in males and 9x, 34x, and 186x MRHD in females relative to the further revised clinical dose of 10mg. The 90% (v/v) PEG400 in water vehicle (control) caused lower body weight and a higher incidence and severity of cortical tubule vacuolation and cortical tubule hyperplasia in the kidney and adrenal vacuolation/hypertrophy of the zona glomerulosa, relative to the water control.

Executive CAC Recommendations and Conclusions:

Rats:

- The Committee found that the study was adequate, noting prior Exec CAC protocol agreement.
- The Committee concurred that there were no drug related neoplasms.

Mouse:

- The Committee found that the study was adequate, noting prior Exec CAC protocol agreement.
- The Committee concurred that there were no drug related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DMEP
/Todd Bourcier, PhD/Team leader, DMEP
/Mukesh Summan, PhD, DABT/Reviewer, DMEP
/Mehreen Hai, PhD/PM, DMEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
08/04/2011

DAVID JACOBSON KRAM
08/04/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
cc: [Mannix, Daniel;](#)
Subject: RE: Dapa
Date: Wednesday, August 03, 2011 9:36:56 AM
Attachments: Foreign Visitors Form.doc

Hi Amy (and Dan),

I'm sorry it's taken me a few days to get back to you. A lot of people have been on leave these last two weeks. Please see our response below to the questions in your correspondence dated August 1, 2011 and summarized in your email below:

Question 1) To follow-up in writing on our email request to meet with the Agency after your internal debrief meeting from the dapagliflozin EMDAC meeting. Ideally we could meet with the Agency the week of 8-Aug-2011 or 15-Aug-2011 as this discussion would help inform what documents we should submit to support a productive discussion on 7-Sep-2011.

FDA Response: We're having a very small internal debrief meeting on Thursday (tomorrow) and another larger one, with the whole review team, on Monday (August 8). We will have more clarity on whether we need to meet with you, after the meeting on Monday. If we decide that a meeting is likely to be productive, we should be able to schedule a call with you quickly.

Question 2) To request the scope of the planned 7-Sep-2011 meeting be expanded to include the overall pharmacovigilance plan with an emphasis on the designs of the CV outcome trial [REDACTED] (b) (4)

[REDACTED] If possible, we would like to have this meeting be face-to-face. The current objective of this meeting is to seek feedback from the Agency on the proposed design of the CV outcome trial to satisfy the Post-marketing Requirement [REDACTED] (b) (4)

[REDACTED] Is this acceptable to the Agency?

FDA Response: We are fine with expanding the scope of the 7-Sep-2011 meeting to include the overall pharmacovigilance plan. However, please note that we usually require that you get the relevant meeting background material to us a month before the meeting, to allow us adequate time for review. We strongly recommend that you provide us with the background material for the expanded topics by at least August 15, otherwise our discussion of those topics may be limited. We are also fine with converting this meeting to a face-to-face meeting. Please e-mail me a list of attendees.

For each foreign visitor, please complete and email me the attached Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access. Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Mehreen Hai: x65073; Lena Staunton: x67522.

Please let me know if you have any further questions.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Friday, July 29, 2011 11:55 AM
To: Chiang, Raymond; Hai, Mehreen
Cc: Marchick, Julie; Mannix, Daniel
Subject: RE: Dapa

Hi Ray and Mehreen,

Just an fyi, today we are sending you a letter (attached to this email) which looks to communicate several things:

- Follows up in writing our request to meet with the Agency after your EMDAC debrief meeting. Ideally we could meet with the Agency the **week of 8-Aug-2011 or 15-Aug-2011** as this discussion would help inform what documents we should submit to support a productive discussion **on 7-Sep-2011**.

- Requests the scope of the planned **7-Sep-2011** meeting be expanded to include the overall pharmacovigilance plan with an emphasis on the designs of the CV outcome trial [REDACTED] (b) (4)

[REDACTED] The current objective of the 7-Sep meeting was to discuss only the design of the CV outcome trial. Considering one aspect of the CV outcome trial is also to assess liver safety and cancers, we thought it would be best to discuss our PV plans to assess these potential risks collectively.

- Informs the Agency of our plans to submit additional briefing materials for the **7-Sep-2011 meeting**

Also, I will be on vacation next week. Dan Mannix will be covering for me. I cc'd him on this email and his phone number is [REDACTED] (b) (6)

Regards,
Amy

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Thursday, July 28, 2011 8:53 AM
To: Jennings, Amy; Hai, Mehreen
Cc: Marchick, Julie
Subject: RE: Dapa

Hi Amy,
Thanks for the email.
We will probably have to get back to you next week because alot of people are out of the office now.
I am sure Mehreen has already brought up the request with the team and will get back to you as soon as possible.

Once the official draft pediatric PK/PD protocol submission is received, it will be forwarded to the team.

ray

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Thursday, July 28, 2011 8:48 AM

To: Hai, Mehreen
Cc: Chiang, Raymond; Marchick, Julie; Jennings, Amy
Subject: RE: Dapa

Hi Ray,

I am just following up on the email correspondence between Mehreen and me last week (below). Do you know if the FDA team is willing to meet with us after your internal debrief? I am trying to plan my vacation next week and want to make sure I am available if the Agency is able and willing to meet with us after their debrief meeting. This will help us understand the Agency's thinking after the adcom to help us plan the best path forward.

Also, as relates to a different communication with Mehreen, yesterday we submitted the dapa draft pediatric PK/PD protocol for the Agency's review (I attached the cover letter)

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Thursday, July 21, 2011 12:36 PM
To: Jennings, Amy
Cc: Chiang, Raymond; Marchick, Julie
Subject: RE: Dapa

Hi Amy,
Yes, we do plan to meeting internally during the week of August 1-5. I will bring up your request for a meeting with the team, and get back to you with our thoughts on the matter.

Also, I will be on leave next week (July 25 -29). If you do have any urgent questions, please contact Ray Chiang at 301-796-1940 or by email at raymond.chiang@fda.hhs.gov. Otherwise, I will be back in the office on August 1, and will be available for any questions you may have.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Thursday, July 21, 2011 11:40 AM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: Dapa

Hi Mehreen,

Thank you for your support and willingness to meet with us as we led up to the Dapa EMDAC. Do you plan to have an internal post-EMDAC meeting? If so, can we possibly meet afterwards? It would be very helpful for us to hear the Agency's thoughts to help us plan the best path forward for dapa?

Thanks
Amy

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/s/

MEHREEN HAI
08/03/2011

Henry, Don

From: Henry, Don
Sent: Friday, July 29, 2011 2:13 PM
To: 'Jennings, Amy'
Subject: NDA 202293 IR comment

Hello Dr. Jennings

We have the following information request from our microbiologist:

Your drug product manufacturing protocol does not include procedures for controlling microbiological quality, and your drug product Specification does not include a microbial limits acceptance criterion. Although your observation (Section 3.2.P.2.5) that dapagliflozin film-coated tablets [REDACTED] (b) (4) is supportive of microbiological quality, it is not in itself sufficient to justify exclusion of a microbial limits criterion. In order to omit finished product microbial limits testing as a release requirement, you should implement manufacturing controls, tests, and acceptance criteria that provide assurance of the microbiological quality for each batch of product, and provide an NDA amendment documenting these changes. Process controls, tests and acceptance criteria should be identified in the batch release criteria, and include, for example:

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch, and
- In-process control parameters [REDACTED] (b) (4) that may affect product quality microbiology.

In addition, microbial limits testing should be performed at the initial time point (at a minimum) on stability samples.

In lieu of changing your manufacturing procedure as noted above, the drug product specification should be modified to include a microbial limits acceptance criterion.

If you have any questions, please feel free to contact me

Don L. Henry
Food and Drug Administration
CDER/Office of New Drug Quality Assessment
Phone: 301-796-4227
Don.Henry@fda.hhs.gov

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/s/

DON L HENRY
08/01/2011



NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010 and received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to the teleconference between representatives of your firm and the FDA on July 7, 2011. The purpose of the meeting was to discuss the requirement to conduct a cardiovascular clinical trial as a post-marketing requirement for dapagliflozin. This discussion was a partial response to the Type C meeting request that you submitted on June 2, 2011, to the Investigational New Drug Application (IND 068652) for this dapagliflozin. A more comprehensive discussion will be held at the teleconference scheduled for September 7, 2011, to address the remaining issues outlined in your meeting request.

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

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes for July 7, 2011 teleconference



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: July 7, 2011, 10:00 – 10:45 AM
Meeting Location: Teleconference

Application Number: NDA 202293
Product Name: Dapagliflozin
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb (BMS)

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products (DMEP)
Mehreen Hai, Ph.D. Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Bristol-Myers Squibb (BMS)

Amy Jennings, PhD	Director, Global Regulatory Sciences-US
Joe Lamendola, PhD	Vice President, US Regulatory Head
Mathias Hukkelhoven, PhD	Senior Vice President, Global Regulatory Sciences
Elisabeth Svanberg, MD, PhD	Vice President, Development Lead- Dapagliflozin
Fred Fiedorek, MD	Vice President, Head of CV & Metabolic Development
James List, MD, PhD	Executive Director, Global Clinical Research - CV/Metabolics

AstraZeneca

Margaret G. Melville	Executive Director, CV, AZ Regulatory Affairs
William Mezzanotte, MD, VP	Global Products Development
Elisabeth Björk, MD, PhD	Vice President, Development
Shamik Parikh, MD	Executive Director, Clinical Development CVGI

1.0 BACKGROUND

The New Drug Application (NDA) for dapagliflozin (an SGL2- inhibitor) was received on December 28, 2010, and is currently under review. The requested indication is for the treatment of type 2 diabetes mellitus (T2DM). At the pre-NDA meeting for this drug product (IND 068652), BMS questioned whether the results of the cardiovascular (CV) meta-analysis that they had conducted would fulfill the CV safety requirements for filing the NDA, with no need to conduct further post-marketing CV trials. FDA informed BMS that they could not agree to the fulfillment of the CV requirements until they had reviewed the meta-analysis report in detail during the NDA review. On May 5, 2011, FDA informed BMS that the Division had made the decision that BMS would need to conduct a dedicated CV clinical trial as a post-marketing requirement (PMR) for dapagliflozin (in the event that it is approved for marketing), and suggested that BMS submit a proposal for such a trial and if they wish, request a Type C meeting to discuss the design of the trial. On June 2, 2011, BMS submitted a meeting request (to IND 068652 for dapagliflozin) along with a synopsis of their dedicated CV trial. Question 1 of the meeting document requested further clarification on the Division's rationale for requiring a dedicated CV trial as a PMR. The teleconference in response to the meeting request was scheduled for September 7, 2011, but it was decided that Question 1 would be address earlier in a separate teleconference, which was scheduled for July 7, 2011.

2. DISCUSSION

Dr. Parks clarified that the Division considers it important for BMS to conduct the dedicated CV trial, not just to assess cardiovascular safety, but also to address other issues that have arisen during the review of this NDA, including those for liver and bone safety and breast and bladder cancer. Dr. Parks acknowledged that the CV meta-analysis was planned and discussed with the Agency prior to being conducted. Despite this, it was felt that the meta-analysis was not adequately designed to conclude that dapagliflozin had met the more stringent CV risk assessment of ruling out the 1.3 upper bound of the 95% confidence interval. The event rate was low reflecting a low risk population studied, and while the Agency had not specified a minimum number of events required to satisfy the CV safety assessment, the low number of events reduces our confidence in concluding that the favorable hazard ratio observed is a true effect. (b) (4)

(b) (4)

BMS reminded FDA that there are two large ongoing trials of two years' duration in high risk patients. Although it is conceivable that data from such trials could be included in a planned meta-analysis, Dr. Parks emphasized that it was in BMS' best interest to conduct its current proposed CV outcomes trial to show CV benefit, in light of the favorable observations in the current meta-analysis. Furthermore, establishing CV benefit might offset concerns such as liver or cancer safety signals. In response to a query from BMS about obtaining glycemic control data from the CV trial, Dr. Parks stated that to date there has been little experience with relying on just one CV trial for glycemic efficacy data. Most programs obtain such data from more traditionally designed programs (i.e., 6-month controlled trials with long-term controlled extension data). (b) (4)

(b) (4)

The main concerns that have been discussed thus far in these trials is maintaining integrity in the ongoing study as interim data are reviewed and submitted to FDA.

BMS also had a few points of discussion regarding the upcoming advisory committee meeting for dapagliflozin (scheduled for July 19, 2011). Specifically, with regards to the cases of breast cancer, BMS wished to point out the FDA briefing package discussed the nine subjects that received dapagliflozin but did not contain mention of the one subject on control. Dr. Parks confirmed that FDA would present the control case as well as the dapagliflozin cases during the slide presentation at the AC meeting, and would clarify this point to the panel members if needed. BMS also informed FDA that they would be submitting updated labeling in August, consisting of an updated Package Insert and Risk Management Plan, as well as a newly-created Medication Guide.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Further discussion on this issue will continue as needed.

5.0 ACTION ITEMS

No action items.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts

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/s/

MEHREEN HAI
07/13/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Friday, July 08, 2011 2:04:13 PM

Hi Amy,

We have another information request for dapagliflozin:

Please provide, by COB July 13th age- and sex-specific exposure data for all Phase 2b and 3 trials, including exposure in trials D1690C00018 and D1690C00019. This will allow us to calculate accurately the standardized incidence ratio of bladder cancer associated with dapagliflozin treatment, compared to SEER, for males at specified age subgroups.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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/s/

MEHREEN HAI
07/08/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa EMDAC- just an update
Date: Thursday, July 07, 2011 3:18:40 PM

Thanks, Amy. I've passed this on to our team.

In response to the email you sent me containing a summary of new information that you may use at the AC, we have the following information request:

Please send us synopses of the reports for Studies MB102035 and MB102066.

Also, in your email below you mention having submitted non-clinical reports for dapa potency. I couldn't find the dog potency report in that submission. Could you please let me know if we're missing something?

Finally, just to confirm what you told us in the tcon this morning, you're going to be submitting an updated Risk Management Plan and a Medication Guide for dapagliflozin? What will be the updated information in the RMP?

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Wednesday, July 06, 2011 9:59 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa EMDAC- just an update

Hi Mehreen,

Attached is the comparison document along with some comments on the Agency's briefing document.

At our meeting tomorrow, is it ok if we also briefly discuss some updates we are planning for our proposed USPI, RMP etc and discuss some key topics related to the dapa EMDAC?

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, July 06, 2011 12:19 PM
To: Jennings, Amy
Subject: RE: Dapa EMDAC- just an update

Hi Amy,
Thanks for this information.
Yes, we would be interested in seeing the comparison once you're done with it.

Thanks!

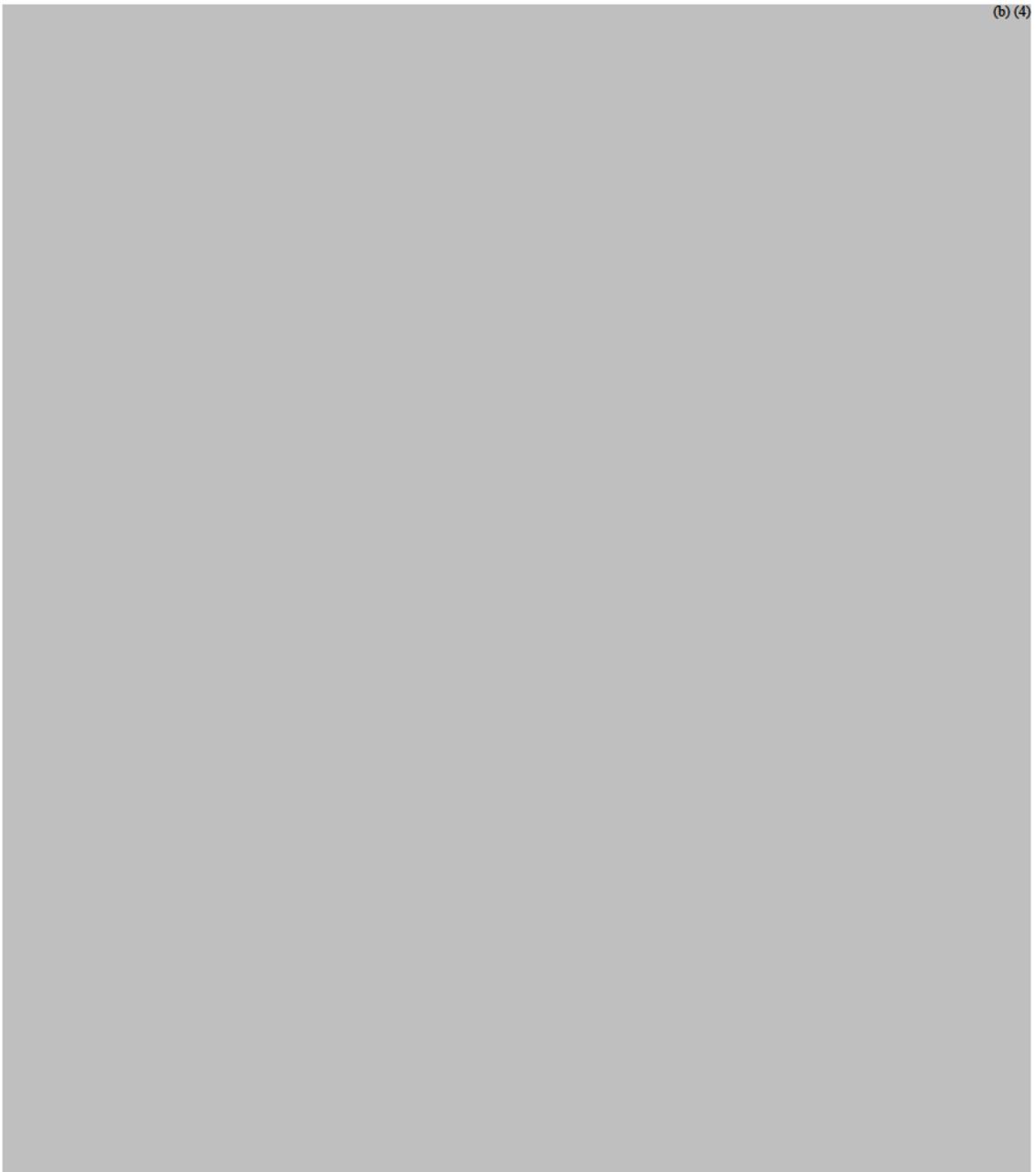
Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Friday, July 01, 2011 12:09 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: Dapa EMDAC- just an update

Hi Mehreen,

I know I have sent information scattered through several emails regarding any new information (e.g., not included in the initial NDA or 4-month safety update) that we may use at the dapa EMDAC. I thought it would be easier to consolidate in one email now that we are getting closer to the EMDAC. If we use the new information in back-up slides, we will acknowledge that the FDA has not seen these data and seek concurrence from the Agency that we can share with the panel. Also, we are currently reviewing our briefing document along with yours to see if there are any inconsistencies that way we are prepared should a question come up. Would you like to see this comparison once we are done?

New information:



3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MEHREEN HAI
07/07/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Tuesday, June 28, 2011 11:39:10 AM

Hi Amy,

We have the following information request for dapagliflozin (NDA 202293):

For patient D1690C00004-4402-6, who met the laboratory threshold for Hy's Law, have you tested this patient for any evidence of seroconversion for hep C at the time of liver test elevation?

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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/s/

MEHREEN HAI
06/28/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa-2 questions: new nonclinical information and pediatrics
Date: Tuesday, June 07, 2011 3:58:44 PM

Hi Amy,
Please see our response to your pediatric query below.

Pediatrics

In the NDA and in a submission dated 5-Aug-2010 (IND 68,652/SN0312), we provided the FDA with our proposed pediatric plans which includes starting the PK/PD study Q3/Q4 2011 (*D1690C00016: A randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of Dapagliflozin in children, 10 to <18 years of age with T2DM receiving one of the three dose levels of Dapagliflozin over the range of 2.5 to 10 mg.*). We are planning to conduct this study in the US and will submit the protocol later this summer. ***Is the Agency ok with us starting with the PK/PD study in pediatrics prior to the NDA action date?***

FDA Response: We suggest that you wait for the Division and the Pediatric Review Committee (PeRC) to review the overall pediatric plan, and for us to review the pediatric PK/PD protocol and offer our comments.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Friday, May 27, 2011 10:28 AM
To: Hai, Mehreen
Cc: Jennings, Amy; Chiang, Raymond
Subject: Dapa-2 questions: new nonclinical information and pediatrics

Hi Mehreen,

Nonclinical

(b) (4)



We plan to submit these reports to the Dapa IND but would like these data to be available at the advisory committee meeting, should such information be requested. ***Would you like me to submit (or cross-reference) these reports to the NDA also?*** In summary these reports will provide

(b) (4)



Pediatrics

In the NDA and in a submission dated 5-Aug-2010 (IND 68,652/SN0312), we provided the FDA with our proposed pediatric plans which includes starting the PK/PD study Q3/Q4 2011 (*D1690C00016: A randomised, multicentre, parallel, single-dose study to explore the pharmacokinetics and pharmacodynamics of Dapagliflozin in children, 10 to <18 years of age with T2DM receiving one of the three dose levels of Dapagliflozin over the range of 2.5 to 10 mg.*). We are planning to conduct this study in the US and will submit the protocol later this summer. ***Is the Agency ok with us starting with the PK/PD study in pediatrics prior to the NDA action date?***

I hope you have a great weekend and nice week off next week!
Amy

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MEHREEN HAI
06/09/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa -edish demodata and liverdata datasets
Date: Tuesday, June 07, 2011 9:19:00 AM

Hi Amy,
No, that's okay, please include all randomized subjects in the datasets.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, June 07, 2011 9:08 AM
To: Jennings, Amy; Hai, Mehreen
Subject: RE: Dapa -edish demodata and liverdata datasets

Hi Mehreen,
Can you confirm if you want us to have only treated subjects b/c we will need to update our program and define doc?
Thanks
Amy

From: Jennings, Amy
Sent: Monday, June 06, 2011 3:24 PM
To: 'Hai, Mehreen'
Cc: Jennings, Amy
Subject: RE: Dapa -edish demodata and liverdata datasets

Hi Mehreen,

I spoke with our statistician and her response to your email just below is , “The dataset contains all randomized subjects. Some subjects were randomized but not treated so that they do not have treatment group names and they do not have starting date and ending date of the treatment. Subjects with the starting date but no ending date are those have not completed the study at time of the 4MSU data cutoff date.” Please let us know if you only want treated subjects. If so, we could delete the randomized but not treated subjects.

We plan to send the revised dataset tomorrow so that both dataset and define document can be sent together.

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Monday, June 06, 2011 2:39 PM
To: Jennings, Amy
Subject: RE: Dapa -edish demodata and liverdata datasets

Hi Amy,

We have another follow-up question regarding the eDISH datasets. The datasets contain records with treatment codes and names entered as missing values. They also contain records where treatment starting dates and/or treatment ending dates are missing.

Could you please fix the data or investigate the quality of the data, along with the requests I sent you earlier today?

Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Monday, June 06, 2011 11:21 AM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Dapa -edish demodata and liverdata datasets

Hi Mehreen,

I will forward to team right away....to your question 1, the answer is yes. The reason for the different times is because someone else zipped the file for me (since I did not know how to do it).

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Monday, June 06, 2011 11:19 AM
To: Jennings, Amy
Subject: RE: Dapa -edish demodata and liverdata datasets

Hi Amy,

We have the following requests/questions regarding the datasets you submitted for eDISH:

1) Just to confirm, the two datasets in the unzipped and the zipped format are identical, right? We were a bit confused because the "last modified" time was different for the two set of files.

2) In the adv.xpt dataset, the required variable ALP and ALP_REF_H was not submitted. Can you please correct this?

3) Please do not submit variable "country" in format "\$country." Instead, submit countries in its full name (text field).

4) You did not provide the definition of "YESNO" format. Please de-format, and instead, submit text string Yes or No.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]

Sent: Friday, June 03, 2011 11:03 PM

To: Hai, Mehreen

Cc: Jennings, Amy

Subject: Dapa -edish demodata and liverdata datasets

Hi Mehreen,

Attached are the demodata and liverdata datasets datasets in transport file format.

Due to compliance reasons we need to change the variable names on ADLV (Liver) datasets to 8 characters. The updated names are as follow:



Due to the size, I will also try to send you a ZIP file. Please let me know if you receive this. We will formally submit next week. We will also provide the narrative dataset and narrative pdf in individual files next week.

Have a great weekend,
Amy

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MEHREEN HAI
06/09/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info request for dapagliflozin
Date: Tuesday, June 07, 2011 4:03:14 PM

Hi Amy,

We have the following information request for dapagliflozin:

=====

1. Please clarify what the accepted insulin regimens were for patients in your add-on insulin study, D1690C00006. You state patients were on ≥ 30 IU for at least eight weeks prior to enrollment, but do not specify if it was long or short acting insulin.

2. In your SCS on page 191 in discussing Events of UTI, you state (b) (4)
[REDACTED]
[REDACTED]. However,
previously on page 185 you stated (b) (4)
[REDACTED]

Please clarify, what serious adverse events (SAEs) occurred in the short term and short and long term placebo treated groups that fall under the Events of UTI category.

3. In response to Question 7 of our information request dated May 26, 2011:
Please provide an analysis of patients in the Phase 2b/3 pool who received glycemic rescue by degree of renal function at the time of rescue (mild, moderate or none). Please include the treatment arm of the patient (control versus dapagliflozin) and also the duration of treatment at the time of rescue for these patients.

On June 2, you sent a table that is almost 200 pages long (we acknowledge that you inquired about the format we required). Can you please summarize this table by completing a table that includes dapagliflozin treated patients and controls and divides them by renal impairment at time of rescue? Please indicate the number of patients in each category and also the mean number of days (with SD) at rescue. The table should roughly look like this:

Renal Impairment at Rescue Dapagliflozin
N/
Mean days to rescue (SD) Control
N/
Mean days to rescue (SD)
Normal
Mild
Moderate
Severe

=====

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
06/09/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa -edish demodata and liverdata datasets
Date: Monday, June 06, 2011 11:13:57 AM

Hi Amy,

We have the following requests/questions regarding the datasets you submitted for eDISH:

1) Just to confirm, the two datasets in the unzipped and the zipped format are identical, right? We were a bit confused because the "last modified" time was different for the two set of files.

2) In the advl.xpt dataset, the required variable ALP and ALP_REF_H was not submitted. Can you please correct this?

3) Please do not submit variable "country" in format "\$country." Instead, submit countries in its full name (text field).

4) You did not provide the definition of "YESNO" format. Please de-format, and instead, submit text string Yes or No.

Thanks, and let me know if you have any questions.

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]

Sent: Friday, June 03, 2011 11:03 PM

To: Hai, Mehreen

Cc: Jennings, Amy

Subject: Dapa -edish demodata and liverdata datasets

Hi Mehreen,

Attached are the demodata and liverdata datasets datasets in transport file format. Due to compliance reasons we need to change the variable names on ADLV(Liver) datasets to 8 characters. The updated names are as follow:



Due to the size, I will also try to send you a ZIP file. Please let me know if you receive this. We will formally submit next week. We will also provide the narrative dataset and narrative pdf in individual files next week.

Have a great weekend,
Amy

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MEHREEN HAI
06/06/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- Info Request-status update
Date: Friday, June 03, 2011 4:28:25 PM

Hi Amy,
I got a response back from our team regarding your May 24 safety assessment. Yes, please go ahead and submit your summary of the results.

Also, we have the following information request:

Please provide the estrogen receptor status information (ER and PR) for the nine breast cancer patients.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Friday, June 03, 2011 10:58 AM
To: Jennings, Amy; Hai, Mehreen
Subject: RE: Dapa- Info Request-status update

Hi Mehreen,

just realized I had an error in my text below... please see change in red. Also, was there any important considerations from your mid-cycle meeting that we should be considering as we plan for adcom, risk management, etc. If possible, maybe we can briefly discuss?

Thanks
Amy

From: Jennings, Amy
Sent: Thursday, June 02, 2011 11:14 PM
To: 'Hai, Mehreen'
Cc: Jennings, Amy
Subject: RE: Dapa- Info Request-status update

Hi Mehreen,

Just wanted to give you an update on where we are with the information requests for dapa and also provide an update on additional data we are planning to include in the EMDAC briefing document.

INFORMATION REQUESTS/SUBMISSIONS PLANNED

- Draft CV outcome trial synopsis w/ Meeting request – *emailed Friday 27-May-2011. Will formally submit to IND 68,652 w/cross reference to NDA this week.*
- CMC request dated 12-May-2011 - *emailed response document 26-May-2011. Due to the size limit, we are not able to attach the requested Master Batch Records and updated Executed Batch Records. They are being submitted as updates to Module 3 Regional section in the formal submission this week.*
- Response to FDA May 20 request (hepatic): *Emailed responses on 24-May-2011. Formal submission planned for this week*
- Response to FDA may 25 request (Clin Pharm): *Target submission planned for middle of June*
- Response to FDA May 26 request (Clinical/stat): *Emailed response to first 5 questions on 27-May-2011 and remaining 3 questions 1-Jun-2011. Formal submission planned this week.*
- Response to FDA May 27 request (eDish datasets/narratives): *Target email by early/middle next week followed by formal submission.*
- Nonclinical pharmacology reports pertaining to Dapa potency vs. other human SGLT isoforms (SMIT, SGLT4, SGLT6) and Transcriptional profiles in kidney, liver, adipose and skeletal muscle of male ZDF diabetic rats following 5 weeks of treatment with Dapagliflozin for the following studies: *target submit to IND (cross-ref to NDA) Mid-Jun-2011*

EMDAC

- Draft EMDAC briefing document: *Provided by email Monday 23-May-2011 (Please let us know if you have any comments by 6-Jun-2011) and the final BMS EMDAC briefing book is due to Paul Tran (FDA) on June 16.*
- In the EMDAC briefing document, Other Safety Findings/ Malignancies Section, we plan to provide data which was included in the initial NDA, and the subsequent 4-month safety update. We also plan to include data from an additional safety assessment for neoplasm events completed as of 24 May 2011 because we consider it is important to review and provide updated information in order to address any evolving benefit/risk concerns. This 24-May-2011 assessment includes additional data that has not yet been provided to the FDA as noted below. It was performed across seventeen Phase 2 or 3 studies and provides additional cumulative treatment time (patient-years of exposure) for patients with these events, (May 24 data-cut: Dapa 4976.80, placebo 2348.02 vs 4-Month safety update date-cut: Dapa 4620.68, placebo 2023.88).
 - Additional long term extension data from ongoing studies. The data-cut for the 4-mo safety update was 15-Oct-2010, so this new data-cut provides ~ 7-months of additional exposure for studies D1690C000004, D1690C000012, and MB102029. D1690C000006 completed in mid. Jan. 2011 so this new data-cut provides ~ 3 months more of additional exposure for this study.
 - Data from two recently concluded study (D1690C00010, add-on to DPP4 study and the mechanism of action study MB102035

The results of this analysis show that with increasing exposure and longer duration, the proportion of subjects with events of malignant and unspecified tumors was similar yet 2 specific types of cancer — bladder cancer in men and breast cancer in women —

are currently out of balance, with more cases occurring in dapagliflozin-treated subjects than in control (briefly summarized below for ease of reference)

- Breast cancer was reported in 10 female patients (9 on dapagliflozin and 1 on control) across seventeen completed Phase 2b and 3 clinical program up to 24-May-2011. One additional case was identified in a patient who remains blinded in an ongoing study.
- Bladder cancer was reported for 7 male of all dapagliflozin-treated patients vs 0 control patients across seventeen completed Phase 2b and 3 studies up to 24-May-2011. Three cases with bladder cancer have been reported in **un**blinded studies (as requested these cases have been provided to the FDA). When these 3 additional cases were unblinded, bladder cancer was reported in 10 male patients (9 on dapagliflozin and 1 on control) across nineteen pooled Phase 2b and 3 studies.

We can provide the FDA with a more detailed summary of the 24-May-2011 results if the Agency would find this useful. Please let us know if such a summary would be of interest to the Agency.

Regards,
Amy

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/s/

MEHREEN HAI
06/03/2011

From: [Chiang, Raymond](#)
To: ["Jennings, Amy"; Hai, Mehreen;](#)
Subject: RE: Dapa Information request
Date: Wednesday, June 01, 2011 11:23:45 AM
Attachments: eDish Dapa IR.doc

Hi Amy,
See responses to your questions in the attached document.
Please confirm receipt of this email.
thanks,
ray

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, May 31, 2011 2:22 PM
To: Chiang, Raymond; Hai, Mehreen
Subject: RE: Dapa Information request

Yes, thanks!

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Tuesday, May 31, 2011 2:12 PM
To: Jennings, Amy; Hai, Mehreen
Subject: RE: Dapa Information request

Amy,
These additional questions are also regarding the eDISH information request, correct?
Sorry, trying to catch up.

ray

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, May 31, 2011 1:55 PM
To: Chiang, Raymond; Hai, Mehreen
Subject: RE: Dapa Information request

Thanks Ray;

We have a few additional questions:

- Should this request be done using the 120 day safety update database?

- Please confirm that 'Subject on Protocol at the Time of exam (Y/N)' means that subject is on study treatment at the time of exam (Y/N).
- For each requested dataset, we plan to put all the phase 2 and 3 studies into one dataset and the study can be easily identified by study ID. Is this acceptable?
- We had reported age at baseline using the age at consent date. Is it OK to use this age for this request?
- Please confirm if it is correct to use the last dose date of study medication for DROPDT for subjects discontinued from study and to use missing for subjects completed study?
- Does 'Investigator identifier' mean Site ID?
- Could you please let us know what information needs to be provided for the investigator description?
- We do not routinely measure the Gamma glutamyl transferase so that we will not include it in the dataset

Thanks

Amy

From: Chiang, Raymond [mailto:Raymond.Chiang@fda.hhs.gov]
Sent: Tuesday, May 31, 2011 1:27 PM
To: Jennings, Amy; Hai, Mehreen
Subject: RE: Dapa Information request

Hi Amy,
I forwarded your email to the Dapagliflozin FDA review team.
I will get back to you soon.
ray

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Tuesday, May 31, 2011 11:59 AM
To: Hai, Mehreen; Chiang, Raymond
Cc: Jennings, Amy
Subject: Dapa Information request
Importance: High

Hi Mehreen and Ray,

We will be able to provide you with the requested liver data and demo data datasets by early next week. By early next week, we will also provide you with the liver narratives in pdf per your requested format. These will be the same narratives already provided in the NDA but will be per your requirements of one

narrative per pdf file.

Considering you will have the narratives in pdf format, do you still require the narrative dataset as this will be essentially the same information? If possible, can you please let me know by today so we can prepare accordingly.

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, May 27, 2011 1:51 PM
To: Jennings, Amy
Subject: Information request

Hi Amy,

We have the following information request for you, regarding the cases of liver related abnormalities.

eDISH as a methodology to determine drug-induced liver injury (DILI) is widely accepted by the drug industry. We are using an internal software tool called eDISH, designed to identify cases of drug-induced liver injury (DILI). We'd like to use this tool with dapagliflozin. In order to do this, we need you to provide us with three SAS datasets and optional PDF files for all 11 Phase 3 trials and the three Phase 2 b trials as well. Note that datasets and/or PDF files for individual studies should be submitted in separate file folders that can be identified by the study numbers or titles. The attached Excel file details the requirements for these SAS datasets.

Can you please give us an estimate of how quickly you can provide us with this requested data? As you can imagine, we need this information as soon as possible. If you have any questions, we can arrange a quick tcon with the eDISH Working Group on our end.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research

Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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1. Considering you will have the narratives in pdf format, do you still require the narrative dataset as this will be essentially the same information?

A: It might not always be the case that the narratives provided in the NDA have been written with sufficient clinical detail to facilitate the evaluation of DILI (drug-induced liver injury) unless they were prepared by physicians or other medical personnel skilled in medical differential diagnosis. Adequate clinical detail and relevance are requested in the eDISH-Data Requirements. Clinical narratives produced by technical staff pulling data verbatim from case-report forms are not acceptable, as they are generally not helpful for the purpose of evaluation of DILI. Not only should the narratives be complete but also informative. It is the quality of the narrative that matters. For this reason, we request appropriate clinical experts prepare the narratives in one or two paragraphs and store them in a SAS dataset with the help from the SAS programmer. The PDF-formatted narratives (which may also include tables of lab results) should be treated as optional and supplemental.

2. Should this request be done using the 120 day safety update database?

A: Yes, please include the most updated information

3. Please confirm that 'Subject on Protocol at the Time of exam (Y/N)' means that subject is on study treatment at the time of exam (Y/N).

A: Yes.

4. For each requested dataset, we plan to put all the phase 2 and 3 studies into one dataset and the study can be easily identified by study ID. Is this acceptable?

A: This is acceptable.

5. We had reported age at baseline using the age at consent date. Is it OK to use this age for this request?

A: We need subjects' birth dates to be reported in the specified format.

6. Please confirm if it is correct to use the last dose date of study medication for DROPDT for subjects discontinued from study and to use missing for subjects completed study?

A: This is correct.

7. Does 'Investigator identifier' mean Site ID?

A: Yes

8. Could you please let us know what information needs to be provided for the investigator description?

A: The purpose for putting this optional field there is to allow for additional information for the field, INVNAM (for investigator's name).

9. We do not routinely measure the Gamma glutamyl transferase so that we will not include it in the dataset

A: This is acceptable. This field is optional.

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/s/

MEHREEN HAI
06/03/2011

From: [Chiang, Raymond](#)
To: ["Jennings, Amy"; Hai, Mehreen;](#)
Subject: RE: Dapa Information request
Date: Tuesday, May 31, 2011 2:47:56 PM
Attachments: [Final Response to Question 2 Dated 2011-05-26- Q2 \(NDA 202-293\).pdf](#)
[2011-05-26-bms-512148-us-fda-questions-clinical-q3.pdf](#)
[2011-05-26-bms-512148-us-fda-questions-clinical-q1.pdf](#)

Hi Amy,
See information request (in black font) below. As always, please respond as soon as possible.
thanks,
ray

Reference is made to your Final Response to Q2 (received May 27, 2011) containing the six requested narratives for discontinuations based on BMD change in Study D1690C00012. Clarify the number of subjects discontinued based on BMD change since the 4-month safety update states that there were actually nine such discontinuations.

Also, based on the study report for D1690C00012, it appears that the criterion for discontinuation was based on change in T-score rather than change in BMD. In order to capture those with a BMD change >5%, submit narratives for the following subjects: D1690C00012-209-10, D1690C00012-203-1, D1690C00012-404-3, D1690C00012-108-8 and D1690C00012-304-29. Note whether these subjects were discontinued from the study.

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/s/

RAYMOND S CHIANG
05/31/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information request
Date: Friday, May 27, 2011 1:48:47 PM
Attachments: eDISHdataRequirement.xls

Hi Amy,

We have the following information request for you, regarding the cases of liver related abnormalities.

eDISH as a methodology to determine drug-induced liver injury (DILI) is widely accepted by the drug industry. We are using an internal software tool called eDISH, designed to identify cases of drug-induced liver injury (DILI). We'd like to use this tool with dapagliflozin. In order to do this, we need you to provide us with three SAS datasets and optional PDF files for all 11 Phase 3 trials and the three Phase 2 b trials as well. Note that datasets and/or PDF files for individual studies should be submitted in separate file folders that can be identified by the study numbers or titles. The attached Excel file details the requirements for these SAS datasets.

Can you please give us an estimate of how quickly you can provide us with this requested data? As you can imagine, we need this information as soon as possible. If you have any questions, we can arrange a quick tcon with the eDISH Working Group on our end.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
05/27/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information request
Date: Thursday, May 26, 2011 11:54:46 AM
Attachments: Dapa info request.pdf

Hi Amy,
Please find attached an information request for NDA 202293 (dapagliflozin). Let me know if you have any questions.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

Please respond to these questions by close of business on Friday, May 27, 2011:

1. When do you plan to submit the 50-week Clinical Study Report for study D1690C00012?
2. For study D1690C00012, please submit narratives for the six subjects who were discontinued due to a BMD change of 5-10%.
3. In the ADDU dataset for D1690C00012, confirm the "RESULTS" variable for all BMD DXA results. It appears that the values are incorrect (whole integers are reported, i.e. 1, 2, instead of values such as 0.897 or 1.482). Resubmit an updated dataset for BMD of the lumbar spine, total hip and femoral neck with updated calculations for change from baseline and percent change from baseline. All other columns should also be included in the updated dataset.
4. Please provide the definitions used to identify cases of bladder cancer. Specifically, were in situ cases included as bladder cancer? SEER data include in situ bladder cancer cases.
5. For all Phase 2b and 3 studies and for all doses of dapagliflozin, please provide total person-time of follow-up after randomization for each of the age brackets in Table 1 (b) (4)
 The table should separate exposed and control subjects and also be separated by gender.

Age Group	Dapagliflozin Breast Cancer Cases	Dapagliflozin Female Person-Time	SEER Female Breast Cancer Rates	Expected Breast Cancer in Dapagliflozin Patients
20-24	0	5.6	0.000016	0.0001
25-29	0	14.3	0.000083	0.0012
30-34	0	28.8	0.000259	0.0075
35-39	0	59.6	0.000589	0.0351
40-44	0	126.8	0.001209	0.1533
45-49	0	229.4	0.001861	0.4269
50-54	1	357.7	0.002258	0.8077
55-59	1	463.6	0.002802	1.2990
60-64	4	409.5	0.003489	1.4287
65-69	1	222.7	0.003942	0.8779
70-74	1	153.7	0.004100	0.6302
75-79	1	43.1	0.004337	0.1869
80-84	0	6.9	0.004223	0.0291
85+	0	1.0	0.003392	0.0034
Total	9	2122.7	-	5.9

SEER data 2003-2007, SEER 17 crude incidence rates by age, females, breast cancer. Obtained from SEER*Stat November 22, 2010

Please respond to these questions by close of business Wednesday June 1.

6. Please identify the treatment arm for the following patients and explain why they are not provided in the database:

- MB102013-90-95 (listed in your Summary of Clinical Safety as a case with liver enzyme elevations and also listed in a subsequent email response to Dr. Hai regarding these cases on Monday, May 09, 2011 7:11 PM)
- MB102034-92-247

7. Please provide an analysis of patients in the Phase 2b/3 pool who received glycemic rescue by degree of renal function at the time of rescue (mild, moderate or none). Please include the treatment arm of the patient (control versus dapagliflozin) and also the duration of treatment at the time of rescue for these patients.

8. In your Summary of Clinical Safety, page 368, you discuss three patients that had pregnancies on dapagliflozin. One was voluntarily terminated. Please provide follow up information and pregnancy outcomes on the other two patients.

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/s/

MEHREEN HAI
05/26/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request for NDA 202293
Date: Wednesday, May 25, 2011 11:30:12 AM

Hi Amy,

We have the following information request for dapagliflozin (NDA 202293):

Reference is made to the 3-May-2011 request from the Agency (via email from Dr. Mehreen Hai) for additional Clinical Pharmacology information and your response dated 9-May-2011.

1. Dapagliflozin has 5 chiral centers which can result in 32 possible diastereomers. Please provide justification for why only 4 of these isomers were evaluated?
- 2) In your response dated 05/09/2011 for Question 1, you refer to a bioanalytical method report entitled "Determination of BMS-512148 and BMS- 801576 in human K2-EDTA Plasma by LC-MS-MS". This report describes a method in which the diastereomers do not interfere with the dapagliflozin peak. However, in that report, clinical plasma samples were not analyzed. In addition, the effect of blank plasma extracts for any interference in the assay was not assessed. **Please provide clear evidence that there is no chiral conversion in vivo. Also, provide the evidence that the bioanalytical assay used for the analysis of clinical samples can separate diastereomers from the dapagliflozin peak.**

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
05/25/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Friday, May 20, 2011 10:56:05 AM

Hi Amy,

We have the following information request for dapagliflozin (NDA 202293):

All questions are regarding liver enzyme elevation patients.

For these cases:

**D1690C00004-4402-6
D1690C00005-6008-10
D1690C00005-6013-3
D1690C00005-7002-4
D1690C00012-403-1
MB102030-9-92**

Please send:

1) Sequential laboratory tests relevant to liver injury / function in tabular format

2) Start and stop dates for all concomitant medications, including study day

3) Work-up of liver injury:

- a) hepatitis serology**
- b) serology for autoimmunity**
- c) EtOH history**
- d) imaging studies**

For patient D1690C00004-4402-6, do you have record of any PT/PTT data? The patient had a liver biopsy and should have had this done. Please report those results.

For patient D1690C00005-6013-3, please see if you can obtain record of the exact nutritional supplements that the patient was on (in addition to St John's Wort and fern).

For patient MB102030-9-92, please let us know whether an Endoscopic retrograde cholangiopancreatography (ERCP) was performed and if so, what the findings were. Also, please let us know if a Hepatobiliary Imino-Diacetic Acid scan (HIDA) was done and submit those results as well.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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MEHREEN HAI
05/20/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Dapa- Info Request (b) (4)
Date: Wednesday, May 18, 2011 12:55:41 PM

Hi Amy,
Please see our response to your follow-up question below:

Our control (b) (4)
was accepted by the FDA during the CMC EoPII meeting (CMC EOP2 meeting minutes, dated 26-Sep-2008, attached). As for IARC limit (b) (4) cited in the FDA question, we are not clear how the (b) (4) limit was obtained based on the (b) (4) daily exposure. Could you please clarify how the (b) (4) limit was derived?

FDA Response: Upon further discussion between the quality review and preclinical teams, we agree that (b) (4) is an acceptable and appropriate specification (b) (4). In reference to the EOPII comment in your question, please note that levels of impurities/degradants acceptable for marketing approval can differ from levels present in pre-market clinical trials.

Please let me know if you have any further questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Thursday, May 12, 2011 6:03 PM
To: Hai, Mehreen

Cc: Jennings, Amy
Subject: Dapa- Info Request (b) (4)

Hi Mehreen,

We have a following clarification request regarding your request below:

Our control (b) (4)

accepted by the FDA during the CMC EoP11 meeting (CMC EOP2 meeting minutes, dated 26-Sep-2008, attached). As for IARC limit (b) (4)

(b) (4) cited in the FDA question, we are not clear how the (b) (4) limit was obtained based on the (b) (4) daily exposure. Could you please clarify how the (b) (4) limit was derived?

Thanks,

Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]

Sent: Thursday, May 12, 2011 10:52 AM

To: Jennings, Amy

Subject: Info Request

Hi Amy,

We have the following non-clinical info request for dapagliflozin (NDA 202293):

A NMT (not more than) (b) (4) specification limit has been set (b) (4) (b) (4) in the drug substance (b) (4) is a known weak carcinogen with an IARC monograph and a tumorigenic dose 50% (TD50) in the rat (b) (4)

(b) (4) This approximates a permitted daily exposure of (b) (4) (b) (4) or approximately (b) (4) Please provide a justification and rationale for setting a (b) (4) specification limit (b) (4).

Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

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MEHREEN HAI
05/18/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Tuesday, May 17, 2011 4:40:37 PM

Hi Amy,

We have the following information request for dapagliflozin (NDA 202293):

Please reply within two business days:

For the two cases that meet Hy's law, D1690C00005-6013-3 and D1690C00004-4402-6, we would like to know the details of the viral serology that was tested. For patient D1690C00005-6013-3, the narrative simply refers to hepatitis serology being negative, but does not specifically list which tests were done. For patient D1690C00004-4402-6, hepatitis C is not mentioned at all. Please clarify exactly which viral hepatitis markers were assessed and describe these results for both patients.

Please reply within one week:

In your *Four Month Safety Update (4MSU)* you report one case of bladder cancer in a 49-year old in a still blinded study "D1690C00018." Please clarify which study this is as it is not listed in your Tabular Listing of Clinical Studies.

In Appendix 330A to your *Summary of Clinical Safety*, you report one case of "Drug Eruption" in a dapagliflozin treated patient. Please send a case narrative on this patient.

Your Analysis Dataset in the *Summary of Clinical Safety* portion of your NDA submission contains a database that appears to contain all Phase 2b and Phase 3 studies. Please confirm this or explain which of your safety "pools" or patient population/studies are included in this database. Also, please provide a total N and exposure time for the patients treated with dapagliflozin and control.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager

***Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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MEHREEN HAI
05/17/2011

2 Page(s) has been Withheld in Full as duplicate copy of email dated May 12, 2011 10:52:10 am immediately following this page

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Info Request
Date: Thursday, May 12, 2011 10:10:26 AM

Hi Amy,
We need all the cases, not just the SAEs.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, May 11, 2011 4:04 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Info Request

Hi Mehreen;

I have a question on your request 3 below:
The majority of the "thyroid neoplasms," involve non-cancerous (non-malignant) conditions and therefore are probably not SAEs (still checking on this). Do you want narratives for non-SAE cases or only for the SAEs?

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, May 06, 2011 2:26 PM
To: Jennings, Amy

Subject: Info Request

Hi Amy,

We have the following info requests for dapagliflozin (NDA 202293):

1) Please provide ASAP the number and percent of subjects with hematuria detected prior to randomization, by treatment group (all dapa, dapa by dose, all comparator, placebo and active control). Provide also number and percent of subjects who had risk factors for bladder cancer (smoking, occupational exposure, chronic cystitis, prior treatment of cancer with Cytosan, etc).

2) We request that bladder cancer cases remain events for expedited reporting to FDA under both the IND and NDA since we are in the midst of considering the benefit-risk of this product for approval and we deem bladder cancer a significant adverse event for which we need to be informed of new cases in a timely fashion.

3) Please consolidate the following into separate reports and submit within two weeks:

Case narratives for thyroid neoplasms

Case narratives for SAEs of pneumonia

Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

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MEHREEN HAI
05/12/2011



NDA 202293

INFORMATION REQUEST

Bristol-Myers Squibb Company
Attention: Amy A. Jennings, Ph.D.
Director, US /Global Regulatory Lead-Dapagliflozin
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your new drug application (NDA) originally submitted on December 28, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your development data suggest that (b) (4) is critical (b) (4) (b) (4) Modify your specification for the excipients (e.g., lactose anhydrous, crospovidone, and microcrystalline cellulose) to ensure that the appropriate grade of material will be used to ensure product quality. Provide the following information:
 - a. A copy of the Certificate of Analysis (CoA) for representative lots of each of the excipients used in drug product manufacturing
 - b. Include a specification for (b) (4) crospovidone.
2. Clarify whether you have evaluated the effect of lot to lot variability in excipient particle size distribution on tablet content uniformity.
3. If available, provide tablet content uniformity by stratified sampling data for commercial scale batches identified in Table 3.2.P.2.3T26. Re-plot the tablet potency data for segment samples against time (Figure 3.2.P.2.3.F25) and discuss the potential (b) (4)
4. (b) (4)

5. Your manufacturing process description does not provide sufficient process details (e.g. equipment type and size, batch size, process parameters). Submit a master batch record or revise section 3.2.P.3.3 to provide a comparably detailed process description to satisfy 21 CFR 314.50 (d)(1)(ii)(c). Your response should include the following information (but not limited to):
 - a. Batch size
 - b. Acceptable (b) (4) operation
 - c. (b) (4)
 - d. (b) (4)
6. Your executed batch records are incomplete as they do not include all drug product operations including (b) (4) film-coating. Provide complete executed batch records for the following 5 and 10 mg strength tablet batches: 0F57331 and 0F577491.
7. Your process description section (Section 3.3.2) states (b) (4)
8. We are in agreement with your proposal regarding not including impurities specification at release. However, describe if there is any potential for generation of these impurities when manufacturing at previously commercially unverified areas of the design space.
9. Describe (b) (4)
10. Your process development section does not contain any information (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief,
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
05/11/2011



NDA 202293

MEETING MINUTES

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010 and received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to the teleconference between representatives of your firm and the FDA on May 5, 2011. The purpose of the meeting was to have a discussion regarding the requirement to conduct a cardiovascular clinical trial as a post-marketing requirement for dapagliflozin.

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

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: May 5, 2011, 3:00 – 3:30 PM
Meeting Location: Teleconference

Application Number: NDA 202293
Product Name: Dapagliflozin
Indication: Treatment of Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb (BMS)

Meeting Chair: Mary Parks, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Mary Parks, M.D. Director, Division of Metabolism and Endocrinology Products
(DMEP)
Mehreen Hai, Ph.D. Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Amy Jennings, Ph.D. (Director, US/Global Regulatory Lead)
Joseph Lamondola, Ph.D. (Vice President, US Regulatory Head)
Mathias Hukkelhoven, Ph.D. (Senior Vice President, Global Regulatory Sciences)

1.0 BACKGROUND

The New Drug Application (NDA) for dapagliflozin (an SGL2- inhibitor) was received on December 28, 2010, and is currently under review. The requested indication is for the treatment of Type 2 Diabetes Mellitus. At the pre-NDA meeting for this drug product (IND 068652), BMS questioned whether the results of the cardiovascular (CV) meta-analysis that they had conducted would fulfill the CV safety requirements for filing the NDA, with no need to conduct further post-marketing CV trials. FDA informed them that they could not agree to the fulfillment of the CV requirements until they had reviewed the meta-analysis report in detail during the NDA review.

2. DISCUSSION

Dr. Parks informed BMS that, after discussion with Dr. Curt Rosebraugh, and with the Division's recent experience with other anti-diabetic products, the Division had made the decision that BMS would need to conduct a dedicated cardiovascular clinical trial as a post-marketing requirement for dapagliflozin (in the event that it is approved for marketing), and suggested that BMS submit a proposal for such a trial. Dr. Parks explained that while the results of the cardiovascular meta-analysis are encouraging, the caveat with the meta-analysis is that it is not prospectively planned and the number of events collected is not extensive. Dr. Parks also explained that a long-term cardiovascular trial will serve to provide more than just cardiovascular safety data: it will provide overall safety data, including that for liver safety and bladder cancer, two safety concerns recently identified by FDA during the review of this NDA. BMS informed FDA that they are in the process of planning a long-term cardiovascular trial, and proposed that they submit a synopsis of these plans, with the intention of getting feedback from the Division on the design of the trial. BMS also inquired whether the required trial, if it is to be used to collect data on liver safety, would need to be powered to detect cases of Hy's Law. Dr. Parks explained that at present, the primary objective of the trial should be cardiovascular safety, and that it is too early in the review to determine whether it needs to be powered for liver safety. However, a prospective analysis for both liver safety and bladder cancer should be part of the trial design.

BMS also inquired about the issues that FDA is likely to discuss at the upcoming advisory committee meeting for dapagliflozin (scheduled for July 19, 2011). Dr. Parks informed BMS that the safety issues are likely to be liver safety, bladder cancer/overall cancer safety and bone safety, and encouraged BMS to present data on the benefits of the drug as well as the risks.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Further discussion on this issue will continue as needed.

5.0 ACTION ITEMS

BMS proposes to submit within approximately two weeks, a synopsis of their planned long-term cardiovascular trial, in order to get feedback from the Division.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts

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/s/

MEHREEN HAI
05/09/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Friday, May 06, 2011 2:02:03 PM

Hi Amy,

We have the following info requests for dapagliflozin (NDA 202293):

1) Please provide ASAP the number and percent of subjects with hematuria detected prior to randomization, by treatment group (all dapa, dapa by dose, all comparator, placebo and active control). Provide also number and percent of subjects who had risk factors for bladder cancer (smoking, occupational exposure, chronic cystitis, prior treatment of cancer with Cytosan, etc).

2) We request that bladder cancer cases remain events for expedited reporting to FDA under both the IND and NDA since we are in the midst of considering the benefit-risk of this product for approval and we deem bladder cancer a significant adverse event for which we need to be informed of new cases in a timely fashion.

3) Please consolidate the following into separate reports and submit within two weeks:

Case narratives for thyroid neoplasms

Case narratives for SAEs of pneumonia

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
05/06/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Info Request
Date: Thursday, May 05, 2011 1:11:45 PM

Hi Amy,
Please see our response to your follow-up questions in red below.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, May 04, 2011 11:56 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Info Request

Hi Mehreen,

We have a few questions on your request:

- Re your request, "...In your Summary of Clinical Safety (SCS), you report five cases across the All Phase 2b and 3 Pool of patients treated with dapagliflozin that met criteria of ALT or AST > 3X ULN and concomitant or subsequent TBL > 2X ULN (within 30 days after discontinuation of study medication). Please send all the narratives for these patients in a consolidated report, and for any other patients in the clinical program that were treated with dapagliflozin that meet these criteria."

In the 4-month safety update (Sequence 0012), we provided consolidated hepatic narratives in Appendix 2 of the hepatic

adjudication report (eCTD location was 5.3.5.3, study tagging file hac-reports- Hepatic Adjudication Report).

Please let me know if this provides you with what you are looking for in the yellow highlighted text above or if you need us to provide anything further.

FDA Response: Yes, this is fine for the highlighted portion.

- Re your request, “It appears that for your active comparator study, D1690C00004 your xpt files (including your pooled xpt file with the Integrated Summary of Safety) and your clinical trial report do not contain any data (efficacy or safety) by dapagliflozin dose. We understand that the blind is being maintained at the study sites and for patients. However, according to your plans, this should have been unblinded to you and in your NDA submission for our review. Please clarify why we are not finding unblinded data or results by dose for safety or efficacy.”

Study D1690C00004 was conducted as a titration study. T2D patients uncontrolled on Metformin were randomized in a double blind fashion to one of the two treatment arms, dapagliflozin or glipizide. Both treatments were titrated in 3 dose levels; 2.5, 5 and 10 mg for Dapa and 5, 10 and 20 mg dose levels for Glipizide. Patients were titrated at 4 week intervals to the next dose level if FPG was ≥ 110 mg/dl. Titration was carried out in the first 18 weeks of the study called the titration period, followed by a 34 week maintenance period when doses were kept constant. 87% of patients in the dapagliflozin treatment group reached the 10 mg dose level compared to 73% of patients in the glipizide treatment group at week 18.

For this reason in the clinical study report, efficacy and safety is summarized by treatment group (Dapa + met vs. Glipizide + Met) and not by dose.

Of the integrated analyses, Study D1690C00004 is included in 2 pools: the Phase 2b/ 3 pool for safety analyses and the cardiovascular meta-analysis. In these 2 pools, data is generally summarized as all dapagliflozin doses pooled and all comparator pooled. However, in the limited analyses where results are provided by dose, the dapagliflozin dose from Study D1690C00004 is counted in the 10 mg dose.

Can you let me know if this addresses your question/request or if you are looking for something further?

FDA Response: We don't need any further information at this time.

- Re your request, “Your pooled analyses show a numeric imbalance in the number of subjects with breast cancer. Provide a table of the safety population regarding known risk factors for breast cancer (BMI, history of smoking, duration of smoking, estrogen use, etc) at baseline or randomization. This table should be organized by treatment type (placebo, dapagliflozin dose) and present the number and percentage of patients that had medical history of these risk factors. ”

In order to understand the known risk factors for breast cancer we propose to use the Phase 2b and 3 Pool. This is the same pool in which analyses for breast cancer were presented in the SCS. The treatment groups presented for this pool were Total Dapa (not by dose) and All Control.

Can you please confirm if this presentation is acceptable for the table your request?

FDA Response: Yes, this is acceptable.

I may have another question tomorrow.

Regards
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, May 04, 2011 11:34 AM
To: Jennings, Amy
Subject: Info Request

Hi Amy,

Please find attached another information request for dapagliflozin (NDA 202293).

Please note the timelines we have requested for a response.

Thanks, and please let me know if you have any questions.

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

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/s/

MEHREEN HAI
05/05/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Info Request
Date: Wednesday, May 04, 2011 11:34:09 AM
Attachments: Dapagliflozin Info Request 4May2011. pdf.pdf

Hi Amy,
Please find attached another information request for dapagliflozin (NDA 202293).
Please note the timelines we have requested for a response.

Thanks, and please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

Please provide the following within one week:

- In your Summary of Clinical Safety (SCS), you report five cases across the All Phase 2b and 3 Pool of patients treated with dapagliflozin that met criteria of ALT or AST > 3X ULN and concomitant or subsequent TBL > 2X ULN (within 30 days after discontinuation of study medication). Please send all the narratives for these patients in a consolidated report, **and for any other patients in the clinical program that were treated with dapagliflozin that meet these criteria.**
 - We have identified two patients that meet these criteria, D1690C00005-6013-3 and D1690C00004-4402-6 and their case narratives. We would like to request any additional clinical information you have on these patients including the details of patient 6013-3's case. Did the patient had choledocholithiasis near the time he was found to have these enzyme elevations? What was the timeline of events with this past medical history and enzyme elevations?
 - What is your rationale to explain why these cases D1690C00005-6013-3 and D1690C00004-4402-6, are not related to dapagliflozin?
- You present bone marker value changes in your SCS Appendix 4C. Only a select few studies are presented for the short term (24 week) results. For the long term extensions only data from MB102013 and MB102014 are presented.
 - Please clarify which bone markers were followed in which of the phase 3 studies.
 - Where are the mean changes with standard deviations (and range) for these studies located in the submission? If they are not in the submission, please construct a table with all measured bone resorption markers and changes at 24 weeks and also another table for the changes seen in the extension studies at 102 weeks. If you cannot pool these data, please present them by study.
- In your SCS on page 258 you state that serum phosphorus levels increased in all treatment groups. You also quote numbers (*0.10, 0.16, and 0.17 mg/dL in the 2.5, 5, and 10 mg groups, respectively and 0.03 change in placebo*). You state this data come from SCS Appendix 68B. The serum phosphorus data are in Appendix 67B and also do not match what you have in the SCS. Please clarify.
- It appears that for your active comparator study, D1690C00004 your xpt files (including your pooled xpt file with the Integrated Summary of Safety) and your clinical trial report do not contain any data (efficacy or safety) by dapagliflozin dose. We understand that the blind is being maintained at the study sites and for patients. However, according to your plans, this should have been unblinded to you and in your NDA submission for our review. Please clarify why we are not finding unblinded data or results by dose for safety or efficacy.

Please provide the following within two weeks:

- Please construct a forest plot of the efficacy results from the 10 phase 3 studies with the primary endpoint of HbA1c (point estimates with 95% CI, and number of subjects per group). Please organize this plot by study type (monotherapy, add on, initial combination, active control and renal impairment).
- Please construct a table for all regularly monitored laboratory parameters (listed on page 317 of your SCS). This table should give the lab, the change from baseline to week 24 for dapagliflozin and for the placebo. It should have the mean +/- SD, and underneath, the median with (minimum, maximum) as seen below:

Laboratory	Dapagliflozin N=150	Placebo N=150
Potassium (mEq/L)	-0.018±0.030 0.000 (-0.076, 0.040)	0.024±0.032 0.000 (-0.039, 0.088)

- Please clarify where the Observed Cases primary endpoint result table is reported for the AstraZeneca phase 3 study reports. For example, for the active comparator study, D1690C00004, this could not be readily located.
- Please construct a table of what were the glycemic rescue criteria in the long term extension periods of the phase 3 studies.
- Please submit a table of patients in your placebo controlled pool reported with urinary tract infection that also had a genital infection (both in any order). Please separate these data by treatment as you do with your other adverse event tables.
- Please send a consolidated report of all the breast cancer patient narratives.
- Your pooled analyses show a numeric imbalance in the number of subjects with breast cancer. Provide a table of the safety population regarding known risk factors for breast cancer (BMI, history of smoking, duration of smoking, estrogen use, etc) at baseline or randomization. This table should be organized by treatment type (placebo, dapagliflozin dose) and present the number and percentage of patients that had medical history of these risk factors.
- In your renal impairment study MB102029, the inclusion criterion was for patients with moderate renal impairment defined as an eGFR (estimated glomerular filtration rate) value in the range of 30 mL/min/1.73m² to 59 mL/min/1.73m². The description of baseline characteristics for this study population shows that 42.2% of patients randomized to dapagliflozin and 48.8% of patients randomized to placebo had baseline eGFR in the mild insufficiency range (≥60 to <90 mL/min/1.73m²). Please justify why almost half of your patients had mild renal insufficiency.
 - Provide a sensitivity analysis of the HbA1c efficacy results for the patients with moderate renal impairment only.

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/s/

MEHREEN HAI
05/04/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request for dapagliflozin
Date: Tuesday, May 03, 2011 9:34:28 AM

Hi Amy,

We have the following information requests for NDA 202293 (dapagliflozin):

Clinical Pharmacology:

Your summary of Clinical Pharmacology (section 2.7.2; page: 207) says, "*The methods were optimized to separate the 4 synthetically available diastereomers (out of 32 diastereomers) of dapagliflozin from the dapagliflozin peak*".

Provide the bioanalytical methods supporting the sentence above and also showing that the diastereomers do not interfere with the dapagliflozin peak.

Also, the summary of Clinical Pharmacology (section 2.7.2; page: 208) says, "*It was also determined that the dapagliflozin peak measured for quantification was not contaminated by any other co-eluting impurities or other diastereomers of dapagliflozin by analyzing some clinical sample extracts using various high resolution HPLC separation methods including chiral chromatography*".

Please provide us the chiral chromatography data supporting that there is no chiral conversion *in vivo* in the clinical samples analysed.

The above listed information should be submitted to the Agency within **3 business days.**

Pharmacology/Toxicology:

For Study DN09008 (Oral Study of Pre- and Post-Natal Development in Rats) that was submitted to IND 068652 on October 15, 2010, please submit the kidney histopathology (microscopic) historical control data for pre- and post-natal studies conducted in the rat. Please submit this data within **one**

week.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
05/03/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request for NDA 202293
Date: Thursday, April 28, 2011 12:06:47 PM

Hi Amy,

We have the following information request/comment for the dapagliflozin NDA:

The drug product specification for the 5 mg and 10 mg tablets should be revised to include a microbial limits release criterion. The revised specification should include acceptance criteria for total aerobic microbial count, total combined yeasts and molds count, and specific pathogens that are appropriate for the product and manufacturing process. The testing methods should conform to the requirements of USP <61>, *Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests*, and USP <62>, *Microbiological Examination of Non-Sterile Products: Tests for Specified Microorganisms*.

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
04/28/2011



NDA 202293

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb
5 Research Parkway
Wallingford, CT 06492-7660

Attention: Amy A. Jennings, PhD
Director, US Regulatory Liaison

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010, received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dapagliflozin Tablets, 5 mg and 10 mg.

We also refer to your January 31, 2011, correspondence, received January 31, 2011, requesting review of your proposed proprietary name (b) (4). We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

The proposed proprietary name, (b) (4) will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your January 31, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Mehreen Hai at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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CAROL A HOLQUIST
04/26/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Information Request for NDA 202293
Date: Tuesday, April 12, 2011 4:46:16 PM

Hi Amy,
Please see our response (in red) to your question regarding Comment #2:

2) Please construct a simple table of your Phase 3 studies (excluding D1690C0012) and the rescue medications used in each study. Do you want a table similar to Table 1 in the SCS just without the phase 2b studies and without D1690C0012?

FDA Response: No, Table 1 from the SCS is adequate for now. You can disregard the request.

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Monday, April 11, 2011 2:15 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Information Request for NDA 202293

Hi Mehreen,

Please see comments /questions in blue next to questions 2 and 3.

Thanks
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, April 08, 2011 3:22 PM
To: Jennings, Amy
Subject: Information Request for NDA 202293

Hi Amy,

We have the following information request for NDA 202293 (dapagliflozin):

- 1) **What was the stratification plan for Active Control Study D1690C00004?**
- 2) **Please construct a simple table of your Phase 3 studies (excluding D1690C0012) and the rescue medications used in each study. Do you want a table similar to Table 1 in the SCS just without the phase 2b studies and without D1690C0012?**
- 3) **On page 157 of your Summary of Clinical Efficacy (SCE) you indicate that forest plots were done in the monotherapy/combination groupings for subgroups. Some of these plots are in the SCE, for the others you refer to Appendix A2.1.2. These ones you refer to could not be located. Please clarify. The forest plots referred to can be found in Appendix A2.4.1. Sorry for the confusion..**
- 4) **For all Phase 3 studies, please submit the SAS code used to conduct all sensitivity analyses for the primary endpoint. Include all needed SAS macros and formats.**

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
04/12/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request
Date: Tuesday, April 12, 2011 1:55:47 PM

Hi Amy,

We have the following information request for the dapagliflozin NDA:

During our review of the population pharmacokinetics (PopPK) report, we have noted that there are differences between the dataset submitted (PKALL.xpt) and the dataset used for your PopPK analysis.

- **PKALL.xpt has 23783 data records and the data set used for the Final PopPK analysis has 15994 records.**
- **Please provide us with the data set that was used for the analysis of your base and final PPK model. Also, please provide us a clear explanation of the reasons for the deleted records in your analysis.**

The above listed information should be submitted to the Agency **within two business days.**

Thanks!

***Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712***

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/s/

MEHREEN HAI
04/12/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request for NDA 202293
Date: Friday, April 08, 2011 3:22:04 PM

Hi Amy,

We have the following information request for NDA 202293 (dapagliflozin):

1) What was the stratification plan for Active Control Study D1690C00004?

2) Please construct a simple table of your Phase 3 studies (excluding D1690C0012) and the rescue medications used in each study.

3) On page 157 of your Summary of Clinical Efficacy (SCE) you indicate that forest plots were done in the monotherapy/combination groupings for subgroups. Some of these plots are in the SCE, for the others you refer to Appendix A2.1.2. These ones you refer to could not be located. Please clarify.

4) For all Phase 3 studies, please submit the SAS code used to conduct all sensitivity analyses for the primary endpoint. Include all needed SAS macros and formats.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
04/08/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Information Request
Date: Thursday, March 31, 2011 3:35:16 PM

Hi Amy,
Please see our response to your question below:

We are aware that full validation is generally not required for compendial methods; however, the suitability of the method should be verified under actual use. In this case, the term validation was intended to refer to all data supporting the suitability of the method for your product, as well as your rationale for the use of disks. Your proposed timeline of two weeks is acceptable.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Thursday, March 31, 2011 11:35 AM
To: Hai, Mehreen
Cc: Jennings, Amy; Chen, Patty
Subject: RE: Information Request

Hi Mehreen,

As requested, we will provide the disintegration method as requested but validation of this method was not performed because the disintegration method <0121> represents the USP compendial method *General Chapter <701>, Disintegration*. Validation of this method was not required according to [21 CFR 211.194(a)(2)] and USP *General Chapter <1225>, Validation of Compendial*

Procedure. We will target to provide this method within the next 2 weeks. Please let me know if this is acceptable.

Thanks,
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Wednesday, March 30, 2011 3:26 PM
To: Jennings, Amy
Subject: Information Request

Hi Amy,
We have the following biopharmaceutics information request for you for NDA 202293 (dapagliflozin):

Please provide the complete disintegration method report (Method 0121) and supporting validation data.

Please provide this information as soon as possible.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
03/31/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request
Date: Wednesday, March 30, 2011 3:24:11 PM

Hi Amy,
We have the following biopharmaceutics information request for you for NDA 202293 (dapagliflozin):

Please provide the complete disintegration method report (Method 0121) and supporting validation data.

Please provide this information as soon as possible.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
03/30/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information Request
Date: Tuesday, March 29, 2011 1:33:55 PM

Hi Amy,

We have the following information request for NDA 202293 (dapagliflozin):

Please state whether the Clinical Event Committee program for dapagliflozin, including referral, processing and adjudication of potential cardiovascular events was the same for the following protocols:

1. **MB 102013**
2. **MB 102014**
3. **MB 102030**
4. **MB 102034**
5. **D160C00004**
6. **D160C00006**

If there were differences in the CEC programs among the protocols, please describe these differences.

For all of the above protocols, please provide all versions of the following and dates when each version became effective:

1. **Dapagliflozin Cardiovascular Adjudication Reference Manual for Primary Investigators and Study Staff**
2. **Clinical Event Committee (CEC) Charter/Manual of Operations: Dapagliflozin Program**

Please submit the requested information to the NDA.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

mehreen.hai@fda.hhs.gov

Ph: 301-796-5073

Fax: 301-796-9712

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/s/

MEHREEN HAI
03/29/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Information request for dapagliflozin
Date: Tuesday, March 29, 2011 1:26:01 PM

Hi Amy,

Please see our response in red below to your questions regarding the AC meeting:

- For previous adcoms I have worked on (different divisions), we shared our briefing book with the FDA ~ 2 months ahead of the adcom for FDA's review to ensure our briefing book is providing the appropriate information based on the planned topics for the adcom, etc. and in some cases had a meeting to review our proposed slides for the adcom.

This is entirely your decision. The ACS has timelines that companies are asked to adhere to. Our division will not require an earlier submission, but we thank you for your consideration.

- Would the Agency be interested in reviewing our briefing document? If so, we are targeting to provide this for your review ~6-May-2011 with requested feedback by 6-Jun-2011? Is this acceptable to the Agency?

We cannot commit to providing feedback by any particular timeframe. Please see our response to the first bullet.

- Would the Agency be interested in a meeting to review our planned presentation? If so, possibly a meeting the week of 6-Jun or Jun 20-23 would work well for us. Please let me know and I will request a meeting.

We typically do not do this.

- In preparing the EMDAC briefing document, it would be helpful to know which areas the Agency is targeting for discussion at the EMDAC. Do you know if/when you can provide this information to us?

We will update you as we get closer to the meeting date.

Please let me know if you have any further questions.

Thanks!

Mehreen Hai, Ph.D.

Regulatory Project Manager

Division of Metabolism & Endocrinology Products

Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, March 23, 2011 6:13 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Information request for dapagliflozin

Hi Mehreen,

It was nice speaking to you today. In response to your request below. The BMS/AZ statisticians will provide me a response tomorrow for your **questions 2 and 3** and they have a question on your **question 1**. I will provide their question to you later today or tomorrow.

As we discussed today, today we submitted the requested information in the filing letter. Please let me know if what we provided does not fully address your requests so we can provide you with what you are looking for. Also as discussed, this week you will receive an ESR for an imbalance observed in bladder cancer. After reviewing this ESR, please let me know if you require further information.

Regarding the EMDAC tentatively scheduled for 19-Jul-2011, I will f/u with Paul Tran regarding the specifics of the EMDAC but wanted to f/u with you on a few items:

- For previous adcoms I have worked on (different divisions), we shared our briefing book with the FDA ~ 2 months ahead of the adcom for FDA's review to ensure our briefing book is providing the appropriate information based on the planned topics for the adcom, etc. and in some cases had a meeting to review our proposed slides for the adcom
 - Would the Agency be interested in reviewing our briefing document? If so, we are targeting to provide this for your review ~6-May-2011 with requested feedback by 6-Jun-2011? Is this acceptable to the Agency?
 - Would the Agency be interested in a meeting to review our

planned presentation? If so, possibly a meeting the week of 6-Jun or Jun 20-23 would work well for us. Please let me know and I will request a meeting.

- In preparing the EMDAC briefing document, it would be helpful to know which areas the Agency is targeting for discussion at the EMDAC. Do you know if/when you can provide this information to us?

Regards
Amy

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/s/

MEHREEN HAI
03/29/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Information request for dapagliflozin
Date: Friday, March 25, 2011 1:19:29 PM

Hi Amy,
Regarding Question 1, your proposal is acceptable.
Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [<mailto:amy.jennings@bms.com>]
Sent: Wednesday, March 23, 2011 10:21 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Information request for dapagliflozin

Hi Mehreen,
To follow up on **question 1**, "In your summary of clinical efficacy (SCE), on page 67, Table 6 lists the demographic baseline characteristics of the Phase 3 studies. Please make a similar table that shows this data by treatment arm (including breakdown by dapagliflozin dose). You can either make one table that contains all study arms and is organized in the same manner (i.e. monotherapy, add on combination, active comparator, etc) or you can make separate tables for the study groupings. If you choose to make one table, please make a separate one for D1690C00012, the body composition study. Your SCE appendices do not appear to have a table like this, as it contains the **individual studies** by study arm demographics, but **not this type of pooling**. **Please submit your response within a week.**"

The BMS/AZ statisticians have the following question:

In response to your request for tables summarizing selected demographic and baseline characteristics by treatment group and study, we would like to confirm that the following will meet your need. We envision that it will not be possible to put more than two studies together on one page so we propose the following tables:

1. Monotherapy studies (Part 1): Study MB102013 (treatment groups used in primary efficacy analysis) and Study MB102032
2. Monotherapy studies (Part 2): Study MB102013 (treatment groups used in exploratory efficacy analysis: PM doses and Group 2 subjects)
3. Add-on Combination studies (Part 1): Studies MB102014 and D1690C00005
4. Add-on Combination studies (Part 2): Studies MB102030 and D1690C00006
5. Active Comparator study: D1690C00004
6. Initial Combination studies: Studies MB102021 and MB102034
7. Body Composition study: D1690C00012
8. Moderate Renal Impairment study: MD102029

For each study, the table will summarize by treatment group the same variables shown in Tables 6 and 7 of the SCE, using the same summary statistics.

Please confirm whether these proposed tables will satisfy your request.
Thank-you.

Regards
Amy

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/s/

MEHREEN HAI
03/29/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: Information request for dapagliflozin
Date: Wednesday, March 23, 2011 9:51:26 AM

Hi Amy,

We have the following information request for dapagliflozin (NDA 202293):

1. In your summary of clinical efficacy (SCE), on page 67, Table 6 lists the demographic baseline characteristics of the Phase 3 studies. Please make a similar table that shows this data by treatment arm (including breakdown by dapagliflozin dose). You can either make one table that contains all study arms and is organized in the same manner (i.e. monotherapy, add on combination, active comparator, etc) or you can make separate tables for the study groupings. If you choose to make one table, please make a separate one for D1690C00012, the body composition study. Your SCE appendices do not appear to have a table like this, as it contains the **individual studies** by study arm demographics, but **not this type of pooling**. **Please submit your response within a week.**

2. Please clarify the following **within 2-3 business days**:

In your primary endpoint tables presented in the SCE, you state the data presented is after rescue (for example, please see table 12).

- Did your rescue patients have LOCF values imputed?
- Are these LOCF values included in these SCE result tables?
- If so, what is meant by “excluding data after rescue”?
- If not, where are your observed cases analyses? We would like to see efficacy data that does not contain imputed values from these groupings.

3. In your SCE, you state in section 1.4.1 that BMS and AZ differed in the main analysis dataset. AZ patients had to have “a non-missing baseline efficacy value and at least one post-baseline efficacy value.” In your study report for MB102013, Table 7.2 states that N was the number of patients with non-missing baseline and Week T values. This appears to

be the case for most, if not all BMS studies. This appears to be the same technique used by AZ. Please clarify the discrepancy **within 2-3 business days**.

Thanks!

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
03/23/2011

From: [Hai, Mehreen](#)
To: ["Jennings, Amy";](#)
Subject: RE: Filing letter
Date: Wednesday, March 09, 2011 2:46:35 PM

Hi Amy,
In response to your questions below:

- Regarding question 3, “For all Phase III studies, provide electronic files with the randomization dates and codes (e.g., Appendix 1.9 in the study report for MB102013), or describe where these variables can be found.”: randomization dates and codes are found in Appendix 1.9 for all BMS study reports (w/study numbers MB102-xxx) and Appendix 12.1.7 for all AZ study reports (w/study numbers D1690C000xx). Is this the information the Agency is looking for or are you requesting we submit a dataset with this information?

FDA Response: We are requesting that you submit an electronic dataset.

- Regarding question 6, “The protocol for study D1690C00004 refers to a “Study Data Management Plan”. Submit this document, and comparable documents for the other Phase III studies.”: For AZ studies (w/study numbers D1690C000xx), the Study Data Management Plan describe the methods used to collect, check, and process clinical data. It also clarifies the roles and responsibilities of the various functions and personnel involved in the data management process. The equivalent document for BMS studies (w/study numbers MB102-xxx) is the BMS Data Review Plan. We are happy to provide these but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us to provide?

FDA Response: Yes, that is what we want.

- Regarding question 9, “The analysis definition document for MB102013 refers to an IVRS-related file called KITASSGN. Submit this file, and comparable files for the other Phase III studies as applicable.”: Submit this file, and comparable files for the other Phase III studies as applicable.”: We have these files for BMS studies (w/study numbers MB102-xxx) and for AZ study D1690C00004. KITASSGN is a SAS dataset containing container assignment data (actual study medications subject received) that was extracted from the IVRS database. We are happy to provide these files but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us

to provide? If you want us to provide these, we propose to provide them as a SAS transport file accompanied with a pdf version of define.doc for each study. Would this be acceptable?

FDA Response: Yes, your proposal is acceptable.

Also, please ignore Request #10 from the filing letter ("In the DEFINE file..."). We have the information we need.

Please let me know if you have any other questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

From: Jennings, Amy [mailto:amy.jennings@bms.com]
Sent: Wednesday, March 09, 2011 12:50 PM
To: Hai, Mehreen
Cc: Jennings, Amy
Subject: RE: Filing letter

Mehreen,

My email had a few typos for study numbers. Please use corrected version below:

We have a few questions on your requests:

- Regarding question 3, "For all Phase III studies, provide electronic files with the randomization dates and codes (e.g., Appendix 1.9 in the study report for MB102013), or describe where these variables can be found.": randomization dates and codes are found in Appendix 1.9 for all BMS study reports (w/study numbers MB102-xxx) and Appendix 12.1.7 for all AZ study reports (w/study numbers D1690C000xx). Is this the information the Agency is looking for or are you requesting we submit a

dataset with this information?

- Regarding question 6, “The protocol for study D1690C00004 refers to a “Study Data Management Plan”. Submit this document, and comparable documents for the other Phase III studies.”: For AZ studies (w/study numbers D1690C000xx), the Study Data Management Plan describe the methods used to collect, check, and process clinical data. It also clarifies the roles and responsibilities of the various functions and personnel involved in the data management process. The equivalent document for BMS studies (w/study numbers MB102-xxx) is the BMS Data Review Plan. We are happy to provide these but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us to provide?
- Regarding question 9, “The analysis definition document for MB102013 refers to an IVRS-related file called KITASSGN. Submit this file, and comparable files for the other Phase III studies as applicable.”: Submit this file, and comparable files for the other Phase III studies as applicable.”: We have these files for BMS studies (w/study numbers MB102-xxx) and for AZ study D1690C00004. KITASSGN is a SAS dataset containing container assignment data (actual study medications subject received) that was extracted from the IVRS database. We are happy to provide these files but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us to provide? If you want us to provide these, we propose to provide them as a SAS transport file accompanied with a pdf version of define.doc for each study. Would this be acceptable?

Thanks
Amy

From: Jennings, Amy
Sent: Wednesday, March 09, 2011 12:39 PM
To: 'Hai, Mehreen'
Cc: Jennings, Amy
Subject: RE: Filing letter

Hi Mehreen,

We have a few questions on your requests:

- Regarding question 3, “For all Phase III studies, provide electronic files with the randomization dates and codes (e.g., Appendix 1.9 in the study report for MB102013), or describe where these variables can be found.”: randomization dates and codes are found in Appendix 1.9 for all BMS study reports (w/study numbers MB109-xxx) and Appendix 12.1.7 for all AZ study reports (w/study numbers D1690C000xx). Is this the information the Agency is looking for or are you requesting we submit a dataset with this information?
- Regarding question 6, “The protocol for study D1690C00004 refers to a “Study Data Management Plan”. Submit this document, and comparable documents for the other Phase III studies.”: For AZ studies (w/study numbers D1690C000xx), the Study Data Management Plan describe the methods used to collect, check, and process clinical data. It also clarifies the roles and responsibilities of the various functions and personnel involved in the data management process. The equivalent document for BMS studies (w/study numbers MB109-xxx) is the BMS Data Review Plan. We are happy to provide these but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us to provide?
- Regarding question 9, “The analysis definition document for MB102013 refers to an IVRS-related file called KITASSGN. Submit this file, and comparable files for the other Phase III studies as applicable.”: Submit this file, and comparable files for the other Phase III studies as applicable.”: We have these files for BMS studies (w/ study numbers MB102-xxx) and for AZ study D1690C00004. KITASSGN is a SAS dataset containing container assignment data (actual study medications subject received) that was extracted from the IVRS database. We are happy to provide these files but wanted to make sure this is what you are looking for since we have not provided these in the past. Can you please confirm this is what you want us to provide? If you want us to provide these, we propose to provide them as a SAS transport file accompanied with a define.doc for each study. Would this be acceptable?

Thanks,
Amy

From: Hai, Mehreen [mailto:Mehreen.Hai@fda.hhs.gov]
Sent: Friday, March 04, 2011 2:52 PM
To: Jennings, Amy
Subject: Filing letter

Hi Amy,
Here's a copy of the 74-day filing letter for dapagliflozin. The paper copy should come to you in the mail in a few days.
Let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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MEHREEN HAI
03/09/2011



NDA 202293

FILING COMMUNICATION

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your New Drug Application (NDA) dated December 27, 2010, received December 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin tablets (5 and 10 mg).

We also refer to your submissions dated January 5, 12, 27, 28 and 31, and February 1 and 16, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **October 28, 2011**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requests by **September 9, 2011**.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

1. There are few patients of African American origin in your clinical database (84% white, 10% Asian, 3% African American). You state in your *Clinical Overview* that available data

suggests that SGLT2 polymorphisms are rare and your data should be applicable to all regions and races. Please submit your references in support of this statement.

2. As some of your studies are ongoing, please clarify your plan to submit updated analyses of cardiovascular safety based on accrued cardiovascular events.
3. For all Phase III studies, provide electronic files with the randomization dates and codes (e.g., Appendix 1.9 in the study report for MB102013), or describe where these variables can be found.
4. For each Phase III study that used block randomization, provide the block size.
5. For each Phase III study that used stratified randomization and/or enrollment, describe where the stratification variable can be found in the data files.
6. The protocol for study D1690C00004 refers to a "Study Data Management Plan". Submit this document, and comparable documents for the other Phase III studies.
7. For study D1690C00004, explain why the following subjects were excluded from the primary efficacy analysis: 2701-31, 3401-2, 4607-1, 4901-1 and 4902-2.
8. For study D1690C00006, explain why the following subjects were excluded from the primary efficacy analysis: 1204-7, 1210-6, 1301-9, 1308-11, 1412-9, 1418-14, 1418-16, 1508-7, 1803-8, 1810-1, 1904-5, 2203-3 and 2209-2.
9. The analysis definition document for MB102013 refers to an IVRS-related file called KITASSGN. Submit this file, and comparable files for the other Phase III studies as applicable.
10. In the DEFINE file for the analysis dataset for MB102013, there is a comment which states "IF SDTM.DM.ARMCD in ("DAPA2.5MG_QAM") THEN ARMCD = "A"...". However, in the tabulation file named DM the variable ARMCD takes different, less granular values than those listed in the note. In light of this discrepancy, explain how the variable ARMCD was derived in the analysis dataset.
11. Submit no later than six months after the initial NDA submission all available stability data for the drug product batches manufactured at the commercial Humacao, Puerto Rico site; these batches are listed in Table 3.2.P.5.4.T01.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, expanded upon, or modified as we review the application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a partial waiver and a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision regarding the partial waiver and/or the partial deferral requests.

If you have any questions, please contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
03/04/2011

From: [Chiang, Raymond](#)
To: ["Jennings, Amy";](#)
cc: [Hai, Mehreen;](#)
Subject: RE: dapagliflozin NDA# 202-293 2.9.11 IR
Date: Wednesday, February 09, 2011 2:17:40 PM

Hi Amy,

See information request (in black font) below from the statistical reviewer. Please confirm receipt.

According to the Core Statistical Analysis Plan, the primary efficacy analysis set for studies conducted by BMS is Randomized Subjects, defined as subjects who receive double-blind study medication. Based on the study reports, however, it appears that the primary efficacy analysis for a number of studies was based on a more restricted analysis set. For the Phase 3 studies conducted by BMS, explain any cases in which treated subjects were excluded from the primary efficacy analysis.

For all of the Phase 3 studies, explain any cases in which the pre-specified (prior to database lock) analysis set was not used for a key efficacy endpoint.

As a FYI, Mehreen Hai has returned and will be taking over this NDA. I will continue processing this NDA for the next week or so, then Mehreen will be the RPM responsible for this NDA. It has been a pleasure working with you, but of course, you are in very good hands with Mehreen.

thanks!
ray

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/s/

RAYMOND S CHIANG
02/09/2011



NDA 202293

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb
Attention: Amy A. Jennings, Ph.D.
Director, US/Global Regulatory Lead
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Dapagliflozin tablet, 5mg and 10 mg

Date of Application: December 27, 2010

Date of Receipt: December 28, 2010

Our Reference Number: NDA 202293

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **February 26, 2011** in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road

Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Consumer Safety Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RAYMOND S CHIANG
01/21/2011

From: Chiang, Raymond
Sent: Tuesday, January 11, 2011 1:21 PM
To: 'Jennings, Amy'
Subject: RE: NDA 202293 information request

Hi Amy,

See information request (in black italics font) from the FDA statistical reviewer:

Information request applies to all Phase 2b and Phase 3 studies.

Submit the SAS code used to create the analysis data sets and to produce the key tables in the clinical study reports, such as those showing the disposition, demographics, concomitant medication, and the findings for the primary and secondary endpoints. Include all needed SAS macros and formats.

Please respond to this information request within two weeks.

thanks!

ray

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/s/

RAYMOND S CHIANG
01/11/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 068652

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences- Metabolic Sciences
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for dapagliflozin (b) (4) (BMS-512148).

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2010. The purpose of the meeting was to discuss the planned New Drug Application (NDA) submission for dapagliflozin (b) (4) (BMS-512148).

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

If you have any questions, call me at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Raymond Chiang, M.S.
Consumer Safety Officer
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

PreNDA Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, November 9, 2010
Meeting Location: 11:00 A.M. to 12:00 P.M., EST

Application Number: IND 068652
Product Name: Dapagliflozin tablet (BMS-512148)
Indication: Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Raymond Chiang, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)

Mary Parks, M.D.	Director
Somya Dunn, M.D.	Clinical Reviewer
Ilan Irony, M.D.	Clinical Team Leader
Amy Egan, M.D., M.P.H	Deputy Director for Safety
Mukesh Summan, Ph.D., DAPT	Pharmacology/Toxicology Reviewer
Raymond Chiang, M.S.	Consumer Safety Officer
Pooja Dharia, Pharm.D.	Regulatory Project Manager
Lina Aljuburi, Pharm.D., M.S.	Chief, Project Management Staff

Office of Clinical Pharmacology

Ritesh Jain, Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2 (DCP2)
Sally Choe, Ph.D.	Clinical Pharmacology Team Leader, DCP2

Office of Biostatistics

Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II (DBII)
Janice Derr, Ph.D.	Statistical Reviewer, DBII

Office of New Drug Quality Assessment

Suong Tran, Ph.D.	CMC Lead, Division of New Drug Quality Assessment III
Xavier Ysem, Ph.D.	Product Quality Reviewer
Angelica Dorantes, Ph.D.	Biopharmaceutics Review Lead

Office of Surveillance and Epidemiology

Margarita Tossa, M.S.	Safety Regulatory Project Manager
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Mary Dempsey

Risk Management Coordinator

Office of Pharmaceutical Science

Steven Fong, Ph.D.

Microbiology Reviewer

Division of Scientific Investigations (DSI)

Susan Leibenhaut, M.D.

Medical Officer

SPONSOR ATTENDEES

Bristol-Myers Squibb Company

Amy Jennings, Ph.D.

Director, US/Global Regulatory Lead-Dapagliflozin

Joseph Lamendola, Ph.D.

Vice President, US Regulatory Head

Margo Herron

Director, US Regulatory and Policy

Elisabeth Svanberg, M.D., Ph.D.

Vice President, Development Lead-Dapagliflozin

Fred Fiedorek, M.D.

Vice President, Global Clinical Research - CV/Metabolics

James List, M.D., Ph.D.

Exec Director, Global Clinical Research -CV/Metabolics

Bruce Leslie, M.D., Director

Global Clinical Research - CV/Metabolics

David Boulton, Ph.D.

Director, Clinical Pharmacology- CV/Metabolics

David Henry, Ph.D.

Exec Director, Global Biometric Sciences, CV/ Metabolics

Lisa Ying, Ph.D.

Associate Director, Global Biometric Sciences

Sergio Ley, M.D.

Director, Safety Physician, Pharmacovigilance and Epi

Jean Whaley, Sc.D.

Group Director, Diabetes Drug Discovery

Mark Tirmenstein, Ph.D.

Senior Research Investigator, Drug Safety Evaluation

Patty Chen, M.S.

Group Manager, Global Regulatory Sciences-CMC

ASTRAZENECA

Mike Angioli, M.S.

Senior Director, Global Regulatory Affairs

Elisabeth Björk M.D., Ph.D.

Vice President Development

Shamik Parikh, M.D.

Executive Director, Clinical Development CV/GI

Jennifer Sugg, M.S.

Principal Statistician

Kristina Johnsson, M.D.

Senior Patient Safety Physician

1.0 BACKGROUND

Dapagliflozin is a SGLT2 inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The dosage form of dapagliflozin is an oral tablet. Dapagliflozin is currently under study for use in T2DM by Bristol-Myers Squibb and AstraZeneca (BMS/AZ).

BMS/AZ proposes to assess efficacy and safety of dapagliflozin in three Phase 2b studies and in eleven Phase 3 studies.

The purpose of this meeting was to discuss the planned NDA for dapagliflozin tablets to be submitted in December 2010.

2. DISCUSSION

CLINICAL

1. The hazard ratio for the primary endpoint of the initial cardiovascular meta-analysis is 0.674 with an upper bound 98% confidence interval of 1.178 (Please see Section 5.3.5 of the preNDA meeting briefing book). BMS/AZ considers these data to fulfill the CV requirements to file the NDA. Furthermore, we also consider these data to preclude the need to conduct further post-marketing CV trials to assess CV safety because this hazard ratio and the more stringent 98% upper CI also meet the <1.3 requirement of the FDA Guidance. As described in the CV SAP (submitted IND 68,652/SN0274), a second meta-analysis was planned (when studies D1690C00018 and D1690C00019 were unblinded and at least 110 events had been accumulated) only if the primary endpoint of the initial CV meta-analysis conducted Sep-2010 had an upper bound confidence interval > 1.8 at a one-sided alpha level of 0.01 (corresponding to a 98% confidence interval) and unacceptable risk had not been ruled out. Given the CV meta-analysis results noted above, we do not intend to perform this second meta-analysis as the FDA Guidance requirements have been met. However, we do plan to provide an updated CV safety analysis in the 4-month safety update as described in the NDA format and content document (IND 68,652/SN0296).

Does the Agency agree that the current CV data fulfill the CV requirements to file the NDA with no need to conduct further post-marketing CV trials according to the current FDA Guidance on assessing CV safety of diabetes drugs?

FDA Response: No, although the cardiovascular (CV) data may be adequate, we cannot agree to their fulfillment of the CV requirements until we have seen your meta-analysis report in detail during the NDA review. In addition to the effect of dapagliflozin on the Major Adverse Cardiovascular Events (MACE) composite endpoint, we will look at the adequacy of the trials, the adjudication process and the effects of dapagliflozin in each of the components of MACE. We will also look at the overall balance between efficacy and safety.

Discussion: No discussion occurred.

2. In view of these encouraging CV meta-analysis results, BMS/AZ are considering potential approaches to demonstrate CV benefit with future clinical trials and/or meta-analyses. As the Agency is aware, two trials in patients with high CV risk are on-going (Studies D1690C00018 and D1690C00019, 950 patients and one year treatment duration per study). Given their size, these studies are expected to provide considerable complementary CV safety information in high CV risk T2DM populations. This additional information would be supplemental to the current adjudicated CV event meta-

analysis qualifying the present NDA submission. Presently, these ongoing studies are planned to conclude during 1H2012. It is feasible to plan further extensions of these ongoing studies and/or expansion or complementation of these studies with additional T2DM patients in order to assess the possible CV benefit of dapagliflozin. (b) (4)

[Redacted]

a.

[Redacted]

(b) (4)



Discussion: No discussion occurred.

3. Considering the summary of safety and efficacy data provided in response to previous Agency requests [e.g., hepatic safety data (IND 68,652/SN0287) and bone safety data (IND 68,652/SN0273)] as well as in the pre-NDA meeting briefing book, does the Agency have any comments that could inform our plans for risk management? If not, can the Agency explain the process and anticipated stage during review when the Agency will provide input on our risk management plans?

FDA Response: A complete review of the proposed risk mitigation strategy in conjunction with the full clinical review after the NDA is submitted will be necessary to determine whether the proposal is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

In order to assist in our review of hepatic safety data, we request that you send in case narratives for any subjects who meet Hy's Law criteria for drug induced liver injury and / or subjects with liver enzymes greater than 5x or 10x the upper limit of normal (ULN). You state that "hepatic disorders leading to discontinuation from study treatment and certain liver laboratory abnormalities will be adjudicated by an independent committee in ongoing Phase 3 studies to determine whether the probability that drug-induced liver injury is the cause of any liver-related abnormalities reported." Ensure that the independent committee adjudicating these events are blinded to treatment assignment, to prevent or reduce potential biases.

Analyze bone fractures as Adverse Events of Special Interest in your NDA, accompanied by narratives and provide separate analyses of changes in metabolic bone markers assessed in the clinical trials.

Analyze elevations in creatinine phosphokinase greater than 10x ULN as well as cases of rhabdomyolysis as Adverse Events of Special Interest in your NDA. These should also be accompanied by case narratives.

Your proposed risk management strategy does not provide sufficient detail to determine that it will be adequate to meet FDAAA criteria and goals, or that a REMS will be necessary to ensure that the benefits of the drug outweigh the risks.

If you plan to submit a REMS with the NDA submission, submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal.

In order to facilitate this submission, we have the following high-level comments. These comments should be considered as general advice only and cannot be considered final until a complete review has been performed.

- **Education or communication provided as part of a REMS should emphasize the safety messages important for the safe use of the product.**
- **Product marketing materials generally are not appropriate to educate about product risks.**

We remind you that a proposed REMS will not be approved as a REMS unless and until we determine that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria.

Discussion: Narratives for hepatic events will be provided in NDA. The hepatic event independent adjudication will be submitted with the 4-month safety update.

FDA requested all bone fracture narratives be included at time of the original NDA submission. The initial NDA submission will contain full narratives for SAEs, discontinuations for fractures due to accidents. For the initial NDA, brief narratives

based on the current database will be provided for non-serious fractures. The sponsor will query the sites for additional information on these events which will be included in updated narratives for the 4-month update.

Narratives for CK elevations >10 ULN will be provided in the initial NDA as requested in the pre-NDA meeting preliminary written feedback letter. The sponsor will likely include these data under Laboratory Investigations, but will include a guide to help the reviewer navigate the safety information.

The sponsor asked when to expect feedback regarding risk management. FDA stated that any potential REMS and PMRs will be discussed with OSE during an internal mid-cycle meeting and we will convey feedback to the sponsor after this internal meeting

4. Follow-up Question included in Response to Comment 2 in response to NDA format and content document (Clinical Pharmacology):

[REDACTED] (b) (4)

[REDACTED] An FDA response to a CMC End of Phase 2 Meeting question on this topic received on 26 September 2008 and in a subsequent email exchange between BMS (29 September 2008) and the FDA (6 October 2008) the FDA indicated that in vitro dissolution bridging studies will be acceptable [REDACTED] (b) (4)

[REDACTED] Based on the feedback, the Sponsor proposes to provide comparative in vitro dissolution data within the Biopharmaceutics Summary Document in support of a biowaiver for the formulation differences between the Phase 3 formulations and the proposed commercial formulations.

Does the Agency concur with our proposal?

FDA Response: The proposed change [REDACTED] (b) (4)

[REDACTED] can be supported with in vitro dissolution data. Therefore, we concur with your proposal of providing in vitro comparative dissolution profile data to support your biowaiver request bridging these formulations.

Discussion: No discussion occurred.

5. Follow-up Question included in Response to Comment 3 in response to the NDA format and content document (Clinical Program):

Given the use rescue/discontinuation based on glycemic criteria in the phase 3 studies, does the Agency consider the planned statistical analyses of HbA1c from long term extension data adequate to demonstrate durability of glycemic effect beyond 24 weeks?

In addition, does the Agency consider assessments of pharmacodynamic effect (glucosuria) throughout the long term extensions to be informative in understanding glycemic durability?

FDA Response: The determination of preserved glycemic effects beyond 24 weeks will be an issue for review. The planned statistical analyses from long-term extension data are adequate (with one possible exception – see next paragraph) but have important limitations with respect to study design and potentially with respect to data quality. Conclusions regarding durability of effect may be limited by the voluntary participation in long term extension studies (thus, not preserving the initial randomization) and by large differential proportion of subjects rescued or discontinued, resulting in substantial amount of data missing. Trials designed to be one year or longer in duration (such as Study D1690C00004) allow for demonstration of glycemic effects beyond 24 weeks, based on a change from baseline in HbA1c to the efficacy timepoint.

Regarding an analysis including measurements after rescue, you state (Comment 3: Clinical Program, p.3) that “if the estimated mean differences between the dapagliflozin treatment groups and control group yield reductions in glycemic parameters when rescue is included, it will provide further support of the effect of dapagliflozin relative to control on glycemic parameters (HbA1c and FPG) in the study population”. The phrase “when rescue is included” seems to indicate you may include rescue as an explanatory effect in the statistical model which is not an appropriate way to adjust for the use of rescue medication.

Glucosuria may be informative in the understanding of glycemic durability, but is considered an exploratory marker, and not a substitute for HbA1c. Comment on the use of the morning spot urinary glucose to creatinine ratio as a potential for unblinding investigators and subjects to the randomized treatment group.

Discussion: The sponsor stated that patient participation in the study extensions was voluntary. The sponsor referred to the 2008 Guidance for Industry: Diabetes Mellitus (Part V.G.3) which describes the use of sensitivity analyses that take account of the effects of rescue medication on the outcome. The sponsor also stated that most patients will eventually require rescue medication.

FDA clarified that the primary concern regarding the evaluation of durability of glycemic effect beyond 24 weeks was the design of the study at the conclusion of the primary endpoint period and the composition of the patient population. This is influenced by the retention of patients in study extensions, and their status regarding the use of rescue medication. For this reason, the evaluation of durability of glycemic effect is a review issue. FDA also clarified that, in general, the proposed statistical analysis models were reasonable. However, including model term(s) for the occurrence of rescue medication is not appropriate and can lead to biased estimates of treatment effect because the occurrence of rescue medication is an outcome itself, not a predictor of outcome. FDA referred the sponsor to the reference by White, et al. (Randomized

clinical trials with added rescue medication: some approaches to their analysis and interpretation, Statistics in Medicine 2001; 20: 2995-3008. This reference describes appropriate statistical approaches which take account of rescue medication. The use of rescue medication can also be evaluated statistically as a secondary outcome.

FDA also reiterated that glycosuria was not a substitute of HbA1c and could therefore not be used to measure glycemic durability.

6. [If our proposals do not satisfy the FDA's request] Follow-up Question included in Response to Comment 4 a and b in response to the NDA format and content document (Summary of Clinical Safety):

As provided in BMS/AZ's response to Comment 4 (a and b), do the above proposals address the Agency's request for additional safety analyses before and after glycemic rescue therapy (4a) and for an exploratory search of the safety database with the current MedDRA version 13.0 to look for potential additional blinded cases for CV adjudication not previously captured through previous MedDRA SMQs preferred terms (4b)?

FDA Response: Yes, these proposals adequately address our requests.

Discussion: No discussion occurred.

7. Follow-up Question included in our response to Comment 9 in response to the NDA format and content document (Datasets):

- a. In response to our question 9 in the NDA format and content document, FDA agreed with our plans to include datasets in the NDA. Since then, we learned we have challenges providing some of the datasets for study MB102010, a placebo-controlled, ascending single-dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of 2.5 to 50 mg doses of dapagliflozin in healthy male Japanese subjects. For this study, we now propose to submit pharmacokinetic datasets only. The CRFs and demographic, safety and pharmacodynamic datasets are constructed in the Japanese language which significantly limits their value. MB102010 is only considered supportive in the US filing as it was conducted in order to initiate dapagliflozin development in Japan to ensure that observations made in dapagliflozin studies already conducted outside of Japan were generally reproducible. No major claims are planned to be made in the proposed USPI on the basis of this study. A similar single ascending dose study (MB102001) in a US healthy subject population with identical endpoints with a wider dose range of dapagliflozin (2.5 to 500 mg) will be included in the filing along with the datasets as will the multiple ascending dose study in Japanese subjects with type 2 diabetes mellitus (MB102025).

Does the Agency agree with our modified dataset plans for Study MB102010?

FDA Response: Yes, we agree.

- b. The eCTD guidance (June 2008) and the instructions on how to present SDTM datasets to FDA (Data specifications v1.5) does not include the submission of a pdf version of the define.xml document. We understand that for ease of review, the FDA would like to have a printed copy of the define.xml to guide them through the datasets. We propose to provide instructions in the reviewer guide on a way to print the define.xml file that is independent of the eCTD viewer tool being used for review.

Does the Agency agree with our proposal?

FDA Response: Yes we agree with this proposal; however, we may request a PDF version of the “Define” document at the time of review.

Discussion: No discussion occurred.

8. Follow-up Question included in Response to Comment 11 in response to the NDA format and content document (4-month Safety Update): Does the Agency agree that the CSR for the drug-drug interaction study between mefenamic acid (a putative uridine diphosphate glucuronosyltransferase (UGT) 1A9 inhibitor) and dapagliflozin can be submitted at the 4-month safety update?

FDA Response: Yes, we agree.

Discussion: No discussion occurred.

CHEMISTRY, MANUFACTURING, and CONTROLS

9. At the time of the NDA filing, BMS will submit 15 months of long-term stability study (LTSS) data for dapagliflozin drug products. During the review period, BMS proposes to submit additional stability data obtained at the 18- and 24-month time points of the LTSS in a single amendment to the NDA (b) (4).
BMS proposes to submit this data no later than six months after the initial submission of the NDA.

Does the Agency concur with BMS' plan to submit additional LTSS data during the NDA review period? Does the Agency concur that submission of this amendment will not affect the review clock?

FDA Response: We do not object to your proposed submission of stability data. Expiry dating of the drug product will be based on the evaluation of the submitted stability data.

Discussion: The sponsor asked whether this submission would impact the review time. FDA concurred that this submission would not affect the review clock. We note that you propose to submit the data no later than 6 months after the initial NDA submission.

10. Quality by Design (QbD) Related Questions: BMS applies QbD principles in the manufacture of dapagliflozin drug substance and drug products and full QbD development knowledge will be provided in the NDA. The following four questions are related to drug product. The information supportive of the following questions will be submitted in the pre-NDA briefing document.
- a. Wavier of Degradant Testing from Drug Product Release: Dapagliflozin drug substance and drug product are stable as demonstrated by the long term stability study (LTSS) results at both room temperature and accelerated storage (40C°/75%) conditions. No degradants are formed during drug product manufacturing. Drug substance impurities present in the drug product are controlled in the drug substance specification. BMS plans to submit batch analysis data and LTSS data for both the drug substance and drug product in support of no degradant testing in the drug release specifications.

Does the Agency concur that degradants testing can be eliminated from dapagliflozin drug product release testing based on the aforementioned supporting data?

FDA Response: Your proposed approach of eliminating degradant testing for drug product release on the basis of drug substance and drug product release and stability data seems reasonable. However, to support this approach we recommend that you include data demonstrating that no degradants will form throughout the proposed design space. Additionally, to aid in our evaluation, provide a discussion of potential drug substance degradation pathways and any related safety concerns.

Discussion: No discussion occurred.

- b. Acceptable Level of Excipient Ranges Utilizing QbD Approach: Dapagliflozin formulation studies indicate that the tablets containing magnesium stearate (b) (4) and crospovidone (b) (4) give acceptable disintegration and dissolution results. The ranges of magnesium stearate and crospovidone are also supported by the excipient compatibility studies. In addition, the long term stability study data has shown no dissolution related changes in the tablets. BMS plans to submit above data in the Quality section of the NDA to support the ranges of magnesium stearate and crospovidone in the tablet formulation.

Does the Agency have any comment on the proposed approach to justify the ranges for magnesium stearate and crospovidone in the drug product formulation based on the aforementioned studied data?

FDA Response: In order to support the proposed ranges for crospovidone and magnesium stearate we recommend that you submit data showing that interaction of the formulation and manufacturing parameters in the design space have no adverse impact on product quality.

Furthermore, the overall dissolution data indicate that the selected dissolution method may not have an adequate discriminating power. Therefore, before we can agree with your approach of justifying with dissolution data the ranges for magnesium stearate and crospovidone in the drug product formulation, we need to evaluate the data supporting the selection of the proposed dissolution method as the most optimal for your product. If dissolution is used in the development of a design space for your drug product, please contact us for early evaluation of the dissolution methodology and acceptance criteria. The selection of dissolution methodology and acceptance criteria is an important factor to consider for development of your design space and RTRT (Real Time Release Testing) approach.

To aid in our evaluation of the proposed dissolution method, provide the dissolution method report including the complete dissolution / release profile data collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., selection of the equipment / apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as the most optimal, should be provided in the report. The dissolution profile should be complete and cover at least 85 percent of drug release of the label amount or whenever a plateau (i.e., no increase over three consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable. The dissolution / release data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug eluted with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.

The method's validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that may have an effect on the dissolution of the drug should also be included in the report. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for the testing of the final product. Include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the method (i.e., method robustness, etc.) and assay

(precision, accuracy, linearity, stability, etc.). The selected method should be discriminatory and sensitive enough to reject lots that would have less than acceptable clinical performance.

Discussion: The sponsor stated that the target for crosopvidone was (b) (4) and for magnesium stearate was (b) (4). FDA stated that the provided data showed (b) (4)

Regarding the magnesium stearate levels, (b) (4)

FDA requested that the sponsor provide the dissolution method development & validation report. The sponsor referred to multiple correspondences with FDA regarding this issue, including an April correspondence regarding using disintegration as a surrogate for dissolution. FDA suggested that for the development of the design space, the sponsor selects a testing variable that is critical for the evaluation of the design space and predicts reliably throughout the entire space; dissolution appears no to be such a variable.

- c. Wavier of Microbial Testing from Drug Product Specifications: Dapagliflozin drug products are manufactured under condition (b) (4)

(b) (4)

Based on the overall risk assessment which considers (b) (4) input materials and manufacturing/ storage conditions, it was determined that microbial testing of the tablets was not necessary at release.

Does the agency concur with the justification that microbial testing is not needed for the drug product specifications?

FDA Response: Microbial testing may be omitted as a release specification provided that the applicant can provide in-process manufacturing controls, tests, and acceptance criteria that demonstrate assurance of the microbiological quality for each batch of product. These process controls, tests and acceptance criteria should be identified in the control strategy, and include, for example:

- Microbial limits data for critical raw materials,
- Microbiological environmental monitoring data for critical processing steps that can be related to the batch,
- In-process control parameters (b) (4) that may affect product quality microbiology.

In addition:

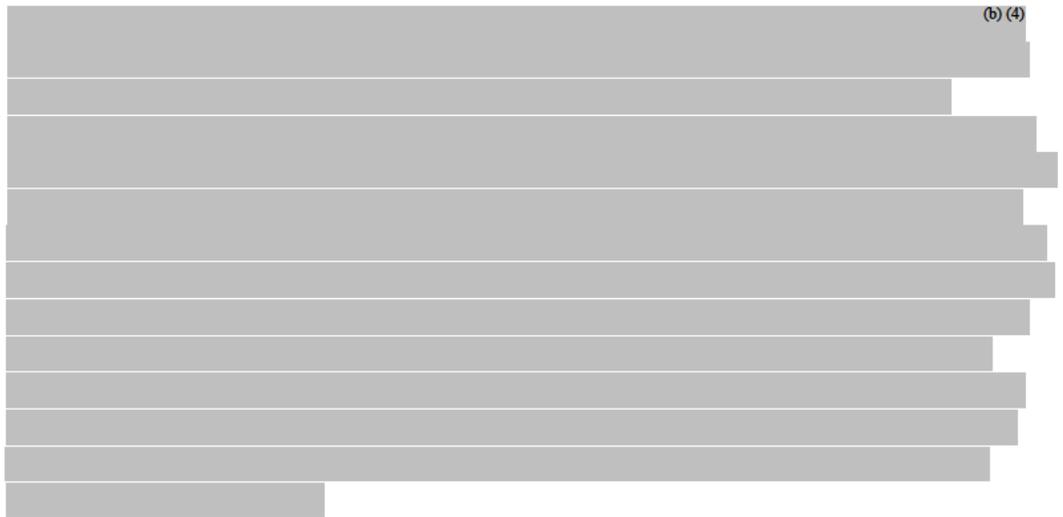
- **Provide historical evidence demonstrating that the drug product consistently meets microbial limits acceptance criteria.**
- **Commit to performing microbial limits testing at the initial time point (at a minimum) on stability samples.**

Approval for elimination of microbial testing as a release test will be contingent on satisfactory responses to the criteria listed above at the time of NDA submission. Control of product (b) (4) will be considered as an in-process control parameter, but will not itself be sufficient justification for waiver of microbial testing.

Discussion: The sponsor stated that they have retrospective data for 12 months and 24 months. FDA requested that the sponsor continue to collect data. The sponsor asked whether data needed to be collected for stability batches. FDA stated that this was a review issue and that microbial testing may still be required as a release specification.

d.

(b) (4)



Does the Agency concur (b) (4)



FDA Response: The proposed approach (b) (4) is acceptable.

(b) (4)





Discussion: No discussion occurred.

ADDITIONAL COMMENTS

Clinical

11. Requests for general study related information and specific Clinical Investigator information
 - a. Include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - 1) Site number
 - 2) Principle investigator
 - 3) Location: City State, Country, to include contact information (phone, fax, email)

Discussion: No discussion occurred.

- b. Include the following information in a tabular format by site in the NDA for each of the completed Phase 3 clinical trials:
 - 1) Number of subjects screened for each site by site

- 2) Number of subjects randomized for each site by site
- 3) Number of subjects treated who prematurely discontinued for each site by site

Discussion: No discussion occurred.

- c. Include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
 - 1) Name, address and contact information of all CROs used in the conduct of the clinical trials
 - 2) The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - 3) The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

Discussion: The sponsor asked for clarification regarding which CROs information was requested for. FDA stated that information would be required for all CROs involved in the clinical trials.

12. Request for Site Level Data

- a. For each site in the pivotal clinical trials provide: Name of primary investigator, accurate address and phone number, e-mail contact
- b. For each pivotal trial include: Sample blank CRF and case report data tabulations for the site with coding key
- c. For each pivotal trial provide: Site-specific individual subject data (“line”) listings from the datasets:
 - 1) Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
 - 2) Line listings by site and subject, of treatment assignment (randomization)
 - 3) Line listings by site and subject, of drop-outs and discontinued subjects with date and reason

- 4) Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
- 5) Line listings by site and subject, of AEs, SAEs, deaths and dates
- 6) Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
- 7) Line listings by site and subject, of the primary and major secondary endpoint efficacy parameters. Limit secondary endpoints to those that support the primary endpoint and are adjusted for an overall type 1 error.
- 8) Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- 9) Line listings by site and by subject, of significant creatinine phosphokinase (>10x ULN), LFT elevations (>5x ULN), or any measured bone marker abnormalities.

Discussion: The sponsor asked what format was being requested regarding the data listings from the datasets. FDA stated, in order to pick which sites were to be inspected, the preferred format was pdf extracted from the SAS datasets. The sponsor asked whether blank case report forms (CRFs) as part of clinical study reports (CSRs) was sufficient. FDA stated that the CRF in each clinical study report was sufficient. The sponsor asked whether information was being requested for patients screened but not randomized. FDA stated yes.

13. Request for Individual Patient Data Listings format:

The Division of Scientific Investigations (DSI) is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

Discussion: FDA stated that usually pivotal trials were inspected, however, if there were a large number of trials, FDA would decide which trials would be inspected. FDA stated the sponsor could request a teleconference regarding this issue.

NonClinical

14. Consider the following when preparing the non-clinical sections for NDA submission:

- a. Include final study reports of the non-clinical studies. Draft reports will not be accepted.
- b. Final carcinogenicity study reports are required at the time of NDA submission, complete with dataset files suitable for FDA Biometrics review. For more information on submitting electronic carcinogenicity data, please contact Karl Lin at karl.lin@fda.hhs.gov.
- c. Histopathology study report sections should describe individual animal findings in addition to the summary tables, complete with incidence and severity scores.
- d. Separate summary toxicology tables by species and highlight drug-related acute, subchronic, and chronic study findings, in-life observations, necropsy findings, and statistical notation where appropriate.
- e. Include a table that lists the drug batches used in non-clinical and clinical studies, including links to impurity/degradant profiles.
- f. Nonclinical studies in PDF file format rather than scanned images of the data are preferred.

Discussion: No discussion occurred.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion

4.0 ACTION ITEMS

No action items identified

5.0 ATTACHMENTS AND HANDOUTS

Attachment 1: Summary Level Clinical Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

Attachment 2: Cardiovascular Event Summary PowerPoint slides presented during the meeting.

20 Page(s) has 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/

RAYMOND S CHIANG
12/02/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 068652

MEETING MINUTES

Bristol-Myers Squibb Company
Attention: Amy A. Jennings, Ph.D.
Director, Global Regulatory Sciences - Metabolic Products
5 Research Parkway
Wallingford, CT 06492-7660

Dear Dr. Jennings:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dapagliflozin (b) (4) (BMS-512148).

We also refer to the teleconference between representatives of your firm and the FDA on December 4, 2009. The purpose of the meeting was to discuss the feedback that we provided in a letter dated August 18, 2009, regarding your proposed cardiovascular analysis plan.

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

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of meeting minutes from teleconference held on December 4, 2009

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: December 4, 2009, 1:30 PM – 2:30 PM
Meeting Location: Teleconference

Application Number: IND 068652
Product Name: Dapagliflozin (b) (4) (BMS-512148)
Indication: Treatment of type 2 diabetes mellitus
Sponsor/Applicant Name: Bristol-Myers Squibb Company

Meeting Chair: Ilan Irony, M.D.
Meeting Recorder: Mehreen Hai, Ph.D.

FDA ATTENDEES

Ilan Irony, M.D.	Diabetes Team Leader, Division of Metabolism & Endocrinology Products (DMEP)
Somya Verma, M.D.	Clinical Reviewer, DMEP
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
David Hoberman, Ph.D.	Statistics Reviewer, Division of Biometrics II
Mehreen Hai, Ph.D.	Regulatory Project Manager, DMEP

SPONSOR ATTENDEES

Bristol-Myers Squibb

Amy Jennings, Ph.D.	Director, Global Regulatory Sciences, Metabolic
Joe Lamendola, Ph.D.	Vice President, Global Regulatory Sciences, Metabolic
James List, MD/Ph.D.	Group Director, Global Clinical Research, CV/Metabolic
Agata Ptaszynska, M.D.	Director, Global Clinical Research, CV/Metabolics
Fred Fiedorek, M.D.	Vice President, Global Clinical Research, CV/Metabolics
Dominic Labriola, Ph.D.	Vice President, Global Biometric Sciences
Lisa Ying, Ph.D.	Associate Director, Global Biometric Sciences, CV/Metabolics
Elisabeth Svanberg, M.D., Ph.D.	Vice President, Development Lead, Dapagliflozin

AstraZeneca

Michael Angioli, M.S.	Senior Director Regulatory Affairs
Jennifer Sugg, M.S.	Principal Statistician, Statistics and Informatics, CV/GI Therapy
Shamik Parikh, M.D.	Executive Director, Clinical Development, CV/GI
Jonathan C Fox M.D., Ph.D., FACC	Vice President, Clinical TA, CVGI
William Mezzanotte, M.D., M.P.H.	Vice President, Development, CV Therapy

1.0 BACKGROUND

Bristol-Myers Squibb (BMS) submitted IND 068652 for dapagliflozin (b) (4) on November 20, 2003. BMS is developing dapagliflozin in alliance with AstraZeneca.

Dapagliflozin is an inhibitor of SGLT-2 (sodium glucose linked transporter type-2), being studied for the treatment of type 2 diabetes mellitus (T2DM).

On June 18, 2009, BMS submitted a meeting request and briefing document with questions regarding their proposed cardiovascular (CV) analysis plan for dapagliflozin. FDA denied the meeting request and instead provided written responses to the questions in the briefing document. On October 19, 2009, BMS submitted a meeting request to discuss and clarify the FDA feedback regarding their CV analysis plan. This meeting request was granted and a teleconference was scheduled for and held on December 4, 2009.

2. DISCUSSION

The Sponsor requested responses to the following questions. The questions are repeated below in italics and a summary of the meeting discussion and post-meeting comments/responses follow in italicized bold.

COMMENT #2

***Question:** Does the Division concur that the adjudicated CV events for the initial dapagliflozin NDA submission can be based on the definitions provided in the current CEC charter (IND 68,652/SN203)?*

***Meeting discussion:** The Division informed BMS that some of the event definitions in the Clinical Events Committee (CEC) charter needed to be revised, such that they are more in line with the FDA's draft recommendations. The Division agreed to provide in writing at a later date our detailed recommendations for these revisions [listed below].*

***Post-Meeting FDA Response:** There are three definitions in your proposed CV Analysis Plan that need revision.*

1. **The definition you propose for Hospitalization for Unstable Angina includes** (b) (4)
(b) (4) **Please amend your definition to no longer include** (b) (4)
(b) (4) **as in the FDA draft recommendation.**
2. **The definition you propose for Stroke is very general and could represent other neurological morbidities such as Bell's palsy. Please amend your definition to the more detailed one provided in our FDA draft recommendation.**
3. **The definition you propose for Revascularization includes** (b) (4)
(b) (4) **Again, this definition is too broad. We would prefer you use the FDA draft definition for "Coronary revascularization;" however, we do not agree with the FDA draft definition** (b) (4) **The** (b) (4),
(b) (4) **should not be part of your revised definition.**

COMMENT #4

Question: Does the Division concur (b) (4)
(b) (4) **in the primary analyses of CV safety? If not, what modifications might be needed** (b) (4)
(b) (4) **in the primary analysis of the CV safety?**

Meeting discussion: BMS presented their rationale (b) (4),
(b) (4) **in primary composite endpoint for the CV safety analysis. The Division reiterated that in order to be consistent with other drug development programs, we would not accept any endpoints other than the traditional MACE, i.e. cardiovascular death, non-fatal myocardial infarction and nonfatal stroke, and possibly unstable angina requiring hospitalization. The Division stated that heart failure and urgent coronary revascularization events would be considered as secondary endpoints** (b) (4)

COMMENT #5

Question: We wish to meet with the Division to discuss the Division's requirements for controlling Type 1 error in the CV safety assessment of dapagliflozin. We would like guidance from the FDA on how to best meet the Division's new CV requirements especially considering these requirements came into effect after we were in the midst of the dapagliflozin phase 3 program and after we sought guidance from the Division on our registrational plans at the end-of phase 2 meeting...

Meeting discussion: BMS informed the Division that they plan to conduct two additional 1-year CV trials starting in early 2010, with patients who have type 2 diabetes and a past history of CV disease. BMS explained that they were considering accumulating additional CV events from these two trials to the currently planned meta-analysis that would be performed at the end of the Phase 3 program in August 2010. The Division recommended against this approach as this would not control Type 1 error, and suggested that BMS submit a revised

statistical analysis plan for further review and discussion. In response to a query from BMS, the Division confirmed that analyses performed for the global filing for dapagliflozin and routine administrative safety surveillance would not incur a statistical penalty.

ADDITIONAL QUESTION

Question: *We have more of an administrative question on the FDA Draft Recommendations for Endpoints and Standardized Data Collection for Cardiovascular Outcome Trials, Appendix 8. In the case of a meta-analysis where the events are coming from the pivotal phase 2/3 studies, would the 5 requested listings need to go into each pivotal study CSR (e.g., add-on to metformin CSR) or would they just be needed in the report for the CV meta-analysis?*

Post-Meeting FDA Response: *You may choose from either of the following two options:*

- 1. You may either have a single document in the CV meta-analysis report with hyperlinks that take the reader directly to the data (whether the data is in the meta-analysis report or in the individual study reports).***
- 2. All the data may be included in the CV meta-analysis report. However, in this scenario, you still should organize the data by study and provide an efficient method to retrieve the corresponding patient narrative.***

3.0 ISSUES REQUIRING FURTHER DISCUSSION

The cardiovascular statistical analysis plan for dapagliflozin needs to be discussed further.

4.0 ACTION ITEMS

- (a)** BMS will submit a revised cardiovascular statistical analysis plan [*submitted by BMS on January 5, 2010*].
- (b)** The Division will provide in writing their recommendations for the revisions of the event definitions in the CEC Charter [*included here with the meeting minutes*].
- (c)** The Division will provide a response to the additional question regarding the FDA Draft Recommendations for Endpoints and Standardized Data Collection for Cardiovascular Outcome Trials, Appendix 8 [*included here with the meeting minutes*].

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-68652

GI-1

BRISTOL MYERS
SQUIBB

Dapaqliflozin (BMS 512148)

(b) (4)

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

/s/

MEHREEN HAI
01/13/2010



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Bristol Myers Squibb
Application Number:	IND 68,652
Product Name:	dapagliflozin (BMS 512148) (b) (4)
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, End of Phase 2 Meeting
Meeting Date and Time:	Thursday, October 9, 2008, 0900 – 1000 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	September 6, 2008

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled as a **face to face meeting** on **Thursday, October 9, 2008**, between **0900 – 1000 ET** between **Bristol Myers Squibb** and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, (301) 796-2055). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

Bristol-Myers Squibb (BMS) submitted Investigational New Drug Application (IND) 68,652 for BMS-512148, (dapagliflozin). BMS-512148 is a novel, potent, highly selective and orally active sodium glucose co-transporter (SGLT2) inhibitor that is being developed for the treatment of type 2 diabetes mellitus (T2DM). Phase III clinical studies are currently ongoing. BMS submitted a request for a CMC End-of-Phase II meeting (August 6, 2008) to discuss proposed starting materials, controls for genotoxic impurities (b) (4) dissolution methodology as well as future development plans for their drug product. The briefing document containing background information for FDA evaluation of the questions submitted in the August 6, 2008 Type B CMC Specific End-of-Phase 2 meeting request to IND 68,652 was submitted on September 5, 2008. The FDA responses to the questions contained in the meeting briefing package are recorded below. These responses will be archived and shared with BMS to promote a collaborative discussion at the meeting.

2.0 DISCUSSION

2.1 Topic 1: Designation of Starting Materials for the Drug Substance Synthesis

2.1.1 An overview of the dapagliflozin drug substance synthesis is provided in the drug substance section of this submission. BMS has designated (b) (4) as the starting materials. Pertinent information to support the starting material designation (b) (4) is provided within. BMS seeks Agency's agreement that the information presented qualifies (b) (4) as starting materials, or we request the FDA to provide guidance on what additional information would be needed to support the proposal.

FDA Response: The proposed drug substance starting materials, (b) (4) are acceptable.

2.2 Topic 2: Control Strategies for Genotoxic Impurities

(b) (4)

2.2.1

(b) (4)

Detailed plans for controlling potential genotoxic impurities (b) (4) are provided in this submission. BMS seeks Agency's concurrence on the proposed control strategies for the potential genotoxic impurities (b) (4).

FDA Response: Judged by the results of the spiking experiment (Table II.3.3.T01), the monitoring of the levels (b) (4)

(b) (4) is adequate from the Chemistry, Manufacture and Controls (CMC) viewpoint. Your proposed control plan (b) (4) is also adequate.

2.3 Topic 3: Proposed Dissolution Method for Dapagliflozin Tablets

2.3.1 Dapagliflozin is a BCS (Biopharmaceutical Classification System) Class III drug substance (high solubility and low permeability) in the physiological pH ranges. Based on studies conducted to assess various dissolution parameters, a dissolution method for dapagliflozin tablet is proposed using the USP Apparatus II (paddle) at 37°C, (b) (4) rpm in 50mM, pH 4.5 acetate buffer medium. Dissolution studies supporting the selection of the proposed methodology are provided within. BMS requests Agency's agreement that the proposed dissolution method is adequate.

FDA Response: The proposed dissolution method, which uses USP Apparatus II (paddle) at 37 °C, (b) (4) rpm in 50 mM, pH 4.5 acetate buffer medium and media volume of 1000 mL, is acceptable. We recommend you provide sufficient scientific justification to support your proposal in the pharmaceutical development section of your NDA.

2.4 Topic 4: Quality by Design (QbD) Approach

2.4.1 The principles of QbD, e.g. identification and evaluation of critical steps and parameters, performance of risk assessments for the identified Critical Process Parameters (CPPs), development of an integrated control strategy and establishment of a significant level of process understanding combined with the basic scientific knowledge, have been used in the development of the drug substance and drug product manufacturing processes. The development work that provides the foundation for understanding the drug substance and drug product manufacturing processes, the rationale for our control strategy are provided.

FDA Response: We have no specific comment on your development plan.

2.5 Topic 5: Bridging Studies for Current Phase III and Commercial Tablets

2.5.1 Current Phase III tablets are (b) (4) diamond shaped, and film coated tablets. They differ from the proposed commercial tablets in shape and color. (b) (4)

(b) (4) BMS plans to conduct comparative dissolution studies to demonstrate the equivalence between the phase III and commercial tablets.

FDA Response: Bridging studies for the Phase III and commercial tablets, which have the same quantitative composition but differ in shape and color, based on comparative dissolution studies to demonstrate equivalence are acceptable. We recommend you provide sufficient scientific justification to support your proposal in your NDA.

2.6 Topic 6: Long-Term Stability Study (LTSS) Plans

2.6.1 The LTSS plans for drug substance and drug product to support the planned NDA filing for dapagliflozin tablets are provided in this submission. The stability studies for drug product will use (b) (4). The stability plans for both drug substance and drug product are based on the guidelines provided in ICH guideline Q1A (R2), "Stability Testing of New Drug Substances and Products," February 2003.

FDA Response: Long-term stability studies (LTSS) (b) (4) in agreement with ICH guideline Q1A (R2), are adequate for the to be proposed NDA. We recommend you provide sufficient scientific justification to support your proposal in your NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time

4.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ali H. Al Hakim, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Linked Applications

Sponsor Name

Drug Name

IND 68652

BRISTOL MYERS
SQUIBB

Dapagliflozin (BMS 512148) (b) (4)

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/s/

SCOTT N GOLDIE

09/26/2008

ALI H AL HAKIM

09/26/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,652

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your Investigational New Drug Application (IND) filed for dapagliflozin (BMS-512148) tablets.

We also refer to the End-of-Phase 2 meeting between representatives of Bristol Myers Squibb Company and AstraZeneca and the FDA on September 11, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Marchick, MPH
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from End-of-Phase 2 meeting held on September 11, 2007

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 11, 2007
TIME: 11:00 AM – 12:00 PM
LOCATION: White Oak Campus, Silver Spring, MD
APPLICATION: IND 68,652
DRUG NAME: Dapagliflozin (BMS-512148) Tablets
TYPE OF MEETING: End-of-Phase 2; Type B

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES:

Division of Metabolism and Endocrinology Products:

Mary Parks, MD	Director
Hylton Joffe, MD, MMSc	Acting Diabetes Clinical Team Leader
Eddie Gabry, MD	Medical Officer
Karen Davis-Bruno, PhD	Pharmacology/Toxicology Team Leader
Lina AlJuburi, PharmD, MS	Chief, Project Management Staff
Julie Marchick, MPH	Regulatory Project Manager

Office of Biostatistics:

Janice Derr, PhD	Biostatistics Reviewer
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Office of Clinical Pharmacology:

Xiaoxiong Jim Wei, PhD	Clinical Pharmacology Reviewer
Sally Choe, PhD	Clinical Pharmacology Acting Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Jean Whaley, ScD	Director, Diabetes Drug Discovery, Discovery Biology, BMS
Bernard Komoroski, PharmD, PhD	Senior Research Investigator, Clinical Discovery, BMS
Elisabeth Svanberg, MD, PhD	Vice President, Full Development Lead, BMS
Fred Fiedorek, MD	Vice President, Global Clinical Research, Cardiovascular and Metabolic Diseases, BMS
Bruce Leslie, MD	Director, Global Clinical Research, BMS
James List, MD, PhD	Director, Global Clinical Research, BMS
Stephanie Moran, MD	Director, Global Clinical Research, BMS
Kalyanee Virswami-Appanna, PhD	Associate Director Biostatistics, Global Biometric Sciences, BMS
Joseph Lamendola, PhD	Vice President, Global Regulatory Sciences, BMS
Pamela Smith, MD	Group Director, Global Regulatory Sciences, BMS

Maria Wagner, PhD	Group Director, Global Regulatory Sciences, BMS
Sara Stults	Director, Regulatory Promotion Compliance, BMS
Heena Pandya, MD	Associate Medical Director, Global Pharmacovigilance, BMS
Greg Cosma, PhD	Executive Director, Drug Safety Evaluation, BMS
Brian Daniels, MD	Global Clinical Development, BMS
Mark Tirmenstein, PhD	Drug Safety Evaluation, BMS
William S. Mezzanotte, MD, MPH	Vice President, Development, Cardiovascular Therapy, AstraZeneca
Shamik Parikh, MD	Medical Science Senior Director, Clinical Research, Cardiovascular, AstraZeneca
Margaret Melville	Senior Global Regulatory Lead, Cardiovascular Therapy Area, AstraZeneca
Susan Harris, MS	Principal Statistician, Biostatistics, AstraZeneca
Glenn F. Carlson, MD	Senior Medical Director, Clinical Pharmacology, AstraZeneca
Teresa P. Dowling, PharmD	Director, Promotional Regulatory Affairs, AstraZeneca

BACKGROUND:

IND 68,652 for dapagliflozin (BMS-512148) tablets was submitted by Bristol-Myers Squibb Company on November 20, 2003. Bristol-Myers Squibb is developing dapagliflozin in alliance with AstraZeneca. Dapagliflozin is an inhibitor of SGLT-2 (sodium glucose linked transporter type-2), being studied for the treatment of type 2 diabetes mellitus (T2DM).

Proposed Phase 3 Clinical Program

Protocol MB102013 is a monotherapy study in drug naïve or minimally treated subjects. A total of 560 subjects are to be enrolled for 24 weeks, with an 18-month extension.

Protocol MB102014 is a combination therapy study in subjects who have failed metformin therapy. A total of 544 subjects are to be enrolled for 24 weeks, with an 18-month extension.

[REDACTED] (b) (4)

Protocol MB102032 is a combination therapy study in subjects who have failed sulfonylurea therapy. A total of 544 subjects are to be enrolled for 24 weeks.

[REDACTED] (b) (4)

Protocol MB102030 is a combination therapy study in subjects taking injectable insulin with or without other oral anti-hyperglycemic agents. A total of 304 subjects are to be enrolled for 24 weeks.

Protocol MB102021 is an initial combination therapy study in drug naïve or minimally treated subjects. A total of 1200 subjects are to be enrolled for 24 weeks.

MEETING OBJECTIVES:

To discuss the results of completed clinical trials and relevant non-clinical studies supporting the proposed Phase 3 clinical development program.

DISCUSSION POINTS:

The Sponsor requested responses to the following questions. The questions are repeated below and the Division's responses provided to the Sponsor on September 10, 2007, follow in bold. The Sponsor's responses provided to the Division on September 11, 2007, prior to the meeting, follow in bold italics. A summary of the meeting discussion is underlined.

Question 1: Nonclinical Pharmacology and Toxicology Program

- a) Does the Agency agree that the Nonclinical Pharmacology program has sufficiently characterized the expected MOA [mechanism of action] and activity of dapagliflozin to support conducting the proposed Phase 3 clinical development program for dapagliflozin?

Division Response: Nonclinical pharmacology data appear to satisfy the requirement of MOA studies.

- b) Does the Agency agree that the completed, ongoing, and planned nonclinical toxicology program adequately characterizes nonclinical findings and supports initiation and completion of the Phase 3 clinical program, which will include study of dosing of patients with T2DM with 2.5 mg, 5 mg, and 10 mg for up to 2 years and will be sufficient for NDA filing and approval?

Division Response: There are a number of pivotal toxicology study reports that have not been received. The Division can address this question after review of the data, currently the Division has reviewed 3-month toxicology data in rat and dog. Preclinical safety concerns with dapagliflozin include QT prolongation found in the 3-month treated dogs, and neurotoxicity that was found in the early toxicity studies with a predecessor of dapagliflozin.

Sponsor Response:

QTc Evaluations

No significant effects on hERG potassium currents or action potential parameters in the rabbit Purkinje fiber assay were observed at dapagliflozin concentrations up to 30 µM (15% inhibition at 2400X of 10 mg human C_{max}). No drug-related cardiovascular (heart rate, blood pressure or ECG) changes were observed in dogs at doses ≤ 250, 180, or 120 mg/kg/day in the 1-, 3-, and 12-month studies, respectively, with the exception of a minimal reversible increase in QTc intervals in males dosed with 180 mg/kg/day in the 3-

month study. Systemic exposures at 120 mg/kg/day in the 12-month study and at 180 mg/kg/day in the 3-month study were 3004X and 4427X (AUC), and 1387X and 1689X (C_{max}), respectively, human exposures at a 10 mg dose. Finally, no drug-related hemodynamic or ECG changes were observed in telemetered dogs following a single oral dose of 30 mg/kg. The extrapolated C_{max} in the telemetry study represents an exposure multiple of approximately 417X the human C_{max} at a 10 mg dose.

Neurotoxicity

The neurotoxic potential of dapagliflozin was assessed in both pivotal and investigative studies in mice, rats and dogs, based on the neurotoxicity (axonopathy) observed in rats and dogs (b) (4) (b) (4). No neurotoxicity has been observed in any study up to the highest dose of dapagliflozin tested, including 1- and 3-month mouse studies (≤ 300 mg/kg/day), 3- and 6-month rat studies (≤ 150 mg/kg/day) or in 3- and 12-month dog studies (≤ 180 mg/kg/day). Evaluations included clinical observations, histopathologic evaluations of central and peripheral nervous tissue and neuroelectrophysiologic evaluations (PNS motor conduction velocity, PNS motor and sensory nerve response, response at the somatosensory cortex, and brainstem auditory evoked potentials). The NOELs for neurotoxicity for the pivotal 6-month study in rats and 12-month study in dogs resulted in systemic exposures that ranged from 1945X (rats) to 3004X (dogs) the AUC at a human dose of 10 mg.

(b) (4)
(b) (4)
(b) (4)
Based on the collective evidence to date, neurotoxicity is not associated with SGLT2 pharmacology (b) (4)

Meeting Discussion: The Sponsor noted that the 12-month dog toxicity study would be submitted within 2 weeks for review.

Question 2: Clinical Pharmacology Program

- a) Does the Agency agree that the completed, ongoing, and planned clinical pharmacology program will be sufficient to support initiation of Phase 3 and subsequent NDA filing and approval of dapagliflozin?

Division Response: The Sponsor's completed, ongoing, and planned clinical pharmacology studies seem sufficient to support initiation of Phase 3. The Division, however, recommends that the Sponsor address the metabolic pathways/major metabolites and CYP inhibition potential of dapagliflozin (according to the draft guidance on Drug Interaction Studies, <http://www.fda.gov/cder/guidance/6695dft.pdf>) adequately. Also, please note the Division's comments under Questions 2b and 2c.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

- b) Does the Agency agree with the approach to utilize a model-based analysis to assess age and gender effects on the exposure of dapagliflozin in subjects with T2DM in lieu of a separate "Age-Gender Study" in healthy subjects?

Division Response: The Sponsor's proposed approach of utilizing a model-based analysis to assess the age and gender effects on the exposure of dapagliflozin seems acceptable.

Sponsor Response: No further discussion is requested.

- c) Does the Agency agree that nonclinical studies in Phase 1 and Phase 2 data evaluating effects of dapagliflozin on QTc intervals, as well as the planned QTc study, as designed, to be conducted in healthy male subjects during Phase 3, will provide sufficient characterization of the safety of dapagliflozin with respect to effects on QTc intervals?

Division Response: No. Please see the Division's response to the proposed QT study protocol.

Sponsor Response: The Sponsor acknowledges the Division's written comments on the propose QT study provided on September 7, 2007, and wishes to inform the Division that several comments have been addressed in the study design (e.g., Williams Square Design). The Sponsor will address the Division's comments in greater detail via a separate, written communication. During the EOP2 [End of Phase 2] meeting, the Sponsor wishes to review and discuss the currently available data applicable to QT.

Detailed clinical results from several early clinical pharmacology trials were submitted to the Division. Of the completed early clinical trials, the most detailed analysis of the effect of dapagliflozin and its active metabolite, BMS-511926, on the QTc interval was performed in a multiple ascending dose study (MB102002). Briefly, healthy subjects received doses of up to 100 mg dapagliflozin for 14 days. Serial ECGs were recorded at 7 time points prior to PK blood draws on Days -1, 1, 7 and 14. Results from this study indicate that treatment with dapagliflozin was not associated with an increased incidence of prolonged QTc intervals or QTc changes from baseline versus for placebo. Additionally, there was no apparent concentration-dependent effect of dapagliflozin on the QTc interval.

The Sponsor believes that the weight of the evidence provided by these available nonclinical and clinical data suggest a low risk for a QT-related safety concern and low risk for a signal to be found in a dedicated QT study. Thus, the Sponsor believes that no further formal assessment of ECGs during Phase 3 would be necessary.

Meeting Discussion: The Sponsor reviewed three non-clinical datasets, which have not yet been submitted to the Division. The Division cannot comment on these studies until the data are submitted and reviewed.

In Phase 3, the Sponsor plans to collect ECGs that will be assessed by investigators at local study sites, with no plan for centralized, formal ECG analyses. The Sponsor stated that the dedicated QT study will be completed in March or April 2008, approximately 6 months into Phase 3.

The Sponsor understands that this approach carries company risk, because a QT prolongation signal could be identified after Phase 3 has started, which would require revisions to the Phase 3 program.

Question 3: Phase 3 Dose Selection

Based on consideration of non clinical pharmacology and toxicity studies, efficacy and safety results of Phase 1, Phase 2A, and Phase 2B clinical studies, together with dose and exposure modeling assessments, BMS and AZ have concluded that doses of 2.5 mg, 5 mg, and 10 mg provide an optimal balance of efficacy and safety.

In phase 2B, dapagliflozin improved glycemic parameters (A1C, FPG) throughout the dose range of 2.5 mg to 50 mg daily, with most of the efficacy realized within the dose range of 2.5 mg to 10 mg. Weight loss was seen at all doses with an apparent relationship to dose. Likely and possible safety concerns of genitourinary infections, increased hematocrit, and hyperphosphatemia were more prominent at doses of 20 mg and above.

Does the Agency agree:

- a) With the selection of once daily doses of 2.5 mg, 5 mg, and 10 mg of dapagliflozin to be studies in the Phase 3 program?

Division Response: No. The potential utility of lower doses of dapagliflozin has not been addressed because the smallest dose tested to date is 2.5 mg/day. From an efficacy perspective, there is no convincing evidence of a relationship between the tested doses of dapagliflozin and the HbA1c response, suggesting that 2.5 mg/day may be at the top of the dose-response curve. From the safety perspective, there is a potential for significant elevations in hematocrit and genitourinary tract infections at higher doses tested and severe hyponatremia at the smallest dose of 2.5 mg. Therefore, the Division strongly urges the Sponsor to explore the HbA1c response and safety of 2 or 3 doses lower than 2.5 mg/day. This could be accomplished by another 12-16 week Phase 2 dose-ranging study prior to the Phase 3 program or by incorporation of lower doses into the Phase 3 program.

In addition, the Division recommends that the Sponsor collect population pharmacokinetic (PK) sampling in the Phase 3 studies. Conducting these exposure-response relationship analyses will add further understanding of the drug's effect on

efficacy and safety parameters, especially since there is not a clear understanding of the dose-response relationship in the Phase 2 studies.

Sponsor Response: The Sponsor acknowledges the Division's responses and recommendations, and wishes to discuss these points further during the EoP2 meeting. In particular, the Sponsor wishes to discuss in greater detail the safety of the proposed doses for evaluation in the Phase 3 program as they relate to outlier analyses for Hct/Hgb, genito-urinary (GU) infections and hyponatremia, based on the data from the Phase 2b study. For example, the impact of dapagliflozin 20 mg and 50 mg doses on Hct/Hgb and GU infections provide support as to why doses between 2.5 mg and 10 mg are proposed for evaluation in Phase 3. Additional details, including concurrent use of diuretics, pre- and post-dosing lab values for serum Na⁺, and probable lab artifacts, regarding the cases of observed hyponatremia at 2.5 mg will be reviewed.

In addition, the Sponsor wishes to discuss the PK/PD relationship and the modeling analyses, including a discussion on those assessments that indicate a decrease in efficacy for doses of 2.5 mg and lower based on PK, glucosuria, and [fasting plasma glucose] FPG.

Meeting Discussion: The Sponsor presented data in response to the Division's concerns regarding elevation in hematocrit, genitourinary tract infections, and hyponatremia. The Sponsor presented a slide (attached) showing hyponatremia in 5 patients in Phase 2b after initiation of 2.5 mg dapagliflozin, and concluded that the Phase 2b findings were most likely artifact. The Sponsor stated that no cases of altered mental status were reported in subjects with hyponatremia.

The Sponsor believes that 2.5 mg is the minimally effective dose based on modeling and reviewed data in support of the dose selection for Phase 3. The Sponsor reviewed the 24-hour pharmacodynamic activity for fasting plasma glucose following administration of doses above 2.5 mg. The Sponsor presented a slide (attached) indicating that with each progressively lower dose, there is a smaller effect on fasting plasma glucose. The Sponsor then discussed exposure-response modeling, indicating that below 2.5 mg, steep drop-offs are predicted for HbA1c and fasting glucose. This model is based on data for administration of doses of 2.5 mg and higher.

The Division stated that there are no definitive data regarding doses lower than 2.5 mg. The Division acknowledged that the currently available safety data do not preclude testing of doses >2.5 mg/day in Phase 3, but strongly recommended that the Sponsor study lower doses of dapagliflozin (which could be evaluated in another Phase 2 study or incorporated into the Phase 3 program). This recommendation is based on the Division's experiences with other products that did not fully explore dose-response relationships. Specifically, there is concern that unnecessarily high doses may show an unfavorable imbalance in the benefit:risk assessment in Phase 3, affecting approvability, without information available about lower doses.

The Sponsor plans a ^{(b) (4)} study of the 1 mg dose in parallel with Phase 3.

- b) With the use of dose matrixing within the Phase 3 program to adequately assess the efficacy, safety, and tolerability of these 3 doses?

Division Response: If 3 doses are selected for Phase 3, it is acceptable that some of the studies include only 2 of the 3 doses. The program is viewed in its totality. The selected doses for a given study should be appropriate for its given population. However, it is important to note that the Sponsor carries some risk with matrixing of the dose. If there is a unique safety signal in an add-on combination study that tests only the higher doses of dapagliflozin, we will not be able to extrapolate safety information about the untested lower doses from other studies that do not have this safety signal.

Sponsor Response: The Sponsor acknowledges Division's response, and wishes to discuss possible clinical trial design approaches in order to provide potential missing information.

- c) With the proposal to further investigate doses lower than 2.5 mg along with 2.5 mg and 5 mg in a PK/PD study (b)(4) examining the lower end of the dose response curve?

Response: The Sponsor's proposed (b)(4) pharmacokinetic/pharmacodynamic (PK/PD) study can be one of the studies that can be considered for investigating dapagliflozin doses below than 2.5 mg/day. However, it seems there is no evidence that the primary PD endpoints of the Sponsor's proposed (b)(4) PK/PD study (i.e., 24-hour urinary glucose excretion, postprandial glucose, and fasting serum glucose) predict long-term glycemic control. Therefore, it is unlikely that the (b)(4) PK/PD study will suffice for Phase 3 study dose selection. A study testing the effect of doses below 2.5 mg/day on HbA1c would provide more reliable data and rationale for Phase 3 study dose selection.

In addition, the Sponsor has stated that there is no log-linear relationship between dapagliflozin dose and HbA1c change from baseline in the Phase 2B trial, MB102008. It is not clear whether the Sponsor has investigated an exposure-response relationship in addition to the dose-response relationship. If that was not conducted previously, the Division recommends the exposure-response relationship analysis to gain further understanding of your drug doses and efficacy parameters before initiation of Phase 3 studies. Also, this effort might aid the Sponsor in evaluating doses below 2.5 mg/day.

Sponsor Response: The Sponsor acknowledges the Division's response and proposed recommendations. As described in our response to the Division's comments to Question 3A, the Sponsor has relied on other PD markers in addition to the established surrogate A1c in order to guide expected efficacy results and the selection of doses chosen for evaluation in the Phase 3 clinical trials. Based on the PD analysis of the completed Phase 2B trial and our efficacy modeling, the Sponsor expects a 1 mg dose to provide sub-optimal efficacy for FPG and A1c. The Sponsor acknowledges the Division's

recommendation for further characterization, and we will conduct a (b)(4) study to evaluate the effects of 1 mg of dapagliflozin. It is the Sponsor's intention to conduct this study in parallel with the Phase 3 program. The Sponsor would be happy to discuss their proposal further at the EoP2 meeting.

Meeting Discussion: Please see the Division's response to Question 3. The Division recommended studying other low doses in addition to 1 mg (e.g., a 1.75 mg dose or 2 mg dose) in a (b)(4) dose-finding study (or by incorporating these doses into the Phase 3 program) using HbA1c as the primary efficacy endpoint.

Question 4: Monotherapy Indication

- a) Does the Agency agree that a single monotherapy study (as proposed with respect to patient population, sample size, number of groups, primary and secondary endpoints, duration, inclusion/exclusion/discontinuation/rescue criteria, and biostatistical approach), in the context of the results of the Phase 2B study and the planned combination therapy studies included in the Phase 3 program, will support approval of an indication for monotherapy?

Response: The Division notes that the Sponsor has only submitted synopses of the proposed Phase 3 studies. The proposed monotherapy study may support a monotherapy indication, provided that the detailed protocols are acceptable and review of the data show a favorable risk-benefit assessment. The Division provides general comments below, but strongly recommends that the Sponsor submit the full study protocols and obtain FDA agreement on the study designs prior to initiation of the clinical studies.

The protocol for the monotherapy study should include a detailed description of the statistical methods used in the design and analysis of data. For example, the statistical methods section of the protocol should fully specify the set of decision rules that will be used to make comparisons among treatment arms.

Sponsor Response: The Sponsor acknowledges the Division's comments and recommendations. The Sponsor wishes to note that they intend to initiate the monotherapy and add-on to metformin studies imminently. The Sponsor still will seek the Division's comments on the protocol. The Sponsor believes that any comments can be addressed through amendment(s) to the protocols. The Sponsor also will be submitting a Core Statistical Analysis Plan (SAP) for review and comment. The study-specific SAP will be designed, using the Core SAP as a foundation.

Division Response (continued): The Division strongly recommends that the Sponsor liberalize their serum creatinine inclusion criteria and actively attempt to enroll a meaningful number of patients with renal impairment in your non-metformin Phase 3 studies. Because dapagliflozin increases urinary glucose excretion, the Sponsor will need to assure the Division that long-term use does not adversely affect renal function in all treated patients, but particularly in patients with underlying renal disease, which is a common long-term manifestation of the intended patient population to be treated

with dapagliflozin. A comprehensive assessment of renal function and electrolytes should be performed frequently throughout the studies and throughout the 18-month extension trials.

Sponsor Response: The Sponsor acknowledges the Division's comments, and agrees to liberalize the serum creatinine inclusion criteria, where appropriate, in the Phase 3 program. Based on an assessment of the totality of the comments, however, this may not completely address the Division's concerns. The Sponsor wishes to discuss in detail the data required to demonstrate the safety and efficacy of dapagliflozin in T2DM patients who have renal impairment.

Meeting Discussion: The Division requested that the Sponsor perform a dedicated renal safety study in patients with mild, moderate, and severe renal impairment. There should be at least 100 patients per group who complete the study. The duration should be at least one year. Population PK data should be collected in the study. The Division recommended that the Sponsor perform a trial to assess pharmacodynamic effect in non-diabetic patients with renal impairment so that the effects of dapagliflozin on urinary glucose excretion are not confounded by hyperglycemia. Regardless of the magnitude of efficacy in renally impaired patients, the Division stressed the need for a dedicated renal safety study because renal impairment is a common complication of diabetes, and many of these patients will likely receive dapagliflozin, if approved. In addition, the Division stated that this renal safety study could also be designed to capture important efficacy information (e.g., using stratification by background anti-hyperglycemic therapy), and recommended that the Sponsor submit the study protocol for review prior to study initiation.

The Division recommends that the Sponsor conduct several 6 month extension studies in addition to the two proposed 18-month extension studies to obtain as much long-term data as possible, particularly because dapagliflozin is a new molecular entity with an unknown safety profile. The Division recommended controlled extensions, but stated that active comparator studies are adequate provided the Sponsor can obtain interpretable efficacy and safety data.

The Sponsor asked whether the results of the extension studies can be submitted after NDA submission. The Division stated that the extension data must be submitted at the time of NDA submission.

Division Response (continued): The maintenance dose of metformin administered during the 18-month extension to the patients initially randomized to placebo should be titrated to the maximally effective dose of 1500 mg/day or higher, as tolerated.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

Division Response (continued): Patients who needed rescue therapy during the first 6 months should not be enrolled in the 18-month extension phase.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

Division Response (continued): Because the patients with baseline HbA1c >10% will be randomized to one of the two doses of dapagliflozin, but not to placebo, baseline HbA1c should not be disclosed to the study investigators nor to the patients except on a need-to-know basis, e.g. if there is a need to break the blind for a given patient.

Sponsor Response: The Sponsor wishes to review the study design with the Division, and, if needed, request further clarification on their comments.

Meeting Discussion: The Sponsor stated that there would be a separate cohort with baseline HbA1c >10% and that subjects in this cohort would be randomized to either 5 mg or 10 mg. Therefore, this cohort would not be included in analysis of the primary endpoint. The Division stated that, given this clarification, it is acceptable for this cohort not to be blinded.

b) [Redacted] (b) (4)

Division Response: [Redacted] (b) (4)

Sponsor Response: The Sponsor wished to address this concern via a separate, written correspondence with the Division.

Question 5: Add-On Combination Therapy Indications

Recognizing that each study is uniquely designed, does the Agency agree that the study design for each of the add-on combination studies as proposed with respect to selected doses, patient populations, sample size, number of groups, primary and secondary endpoints, duration, inclusion/exclusion/ discontinuation/rescue criteria, and biostatistical approach, will support approval of the proposed indications for add combination therapy with:

- Metformin;
- Sulfonylurea;
- TZD;
- DPP-4 inhibitor, and;
- Insulin?

Division Response: The Division agrees in principle, provided that the detailed protocols are acceptable and review of the data show a favorable risk-benefit assessment. As mentioned above, the Division strongly recommends that the Sponsor liberalize the serum creatinine inclusion criterion and actively attempt to enroll a meaningful number of patients with renal impairment in the non-metformin Phase 3 studies.

The protocol for the add-on combination studies should include a detailed description of the statistical methods used in the design and analysis of data. For example, the statistical methods section of the protocol should fully specify the set of decision rules that will be used to make comparisons among treatment arms.

Sponsor Response: The Sponsor acknowledges the Division's recommendations, and agrees to liberalize the serum creatinine inclusion criteria, where appropriate. In addition, the Sponsor agrees to provide the Core SAP for review and comment for all of the Phase 3 studies in the program.

Question 6: Initial Metformin Combination Therapy Indication

Does the Agency agree that the initial combination therapy with metformin study, as proposed with respect to design, patient population, sample size, number of groups, primary and secondary endpoints, duration, inclusion/exclusion/ discontinuation/rescue criteria, and biostatistical approach,

[REDACTED] (b) (4)

Division Response: The Division prefers that this study be postponed until the safety of dapagliflozin is established as a monotherapy and as add-on to metformin. [REDACTED] (b) (4)

[REDACTED] The Division is moving away from granting "initial treatment" indications for anti-diabetic drugs. Reasons for this approach include (a) the lack of data showing long-term benefit of using one initial treatment strategy over another, (b) the Division's desire to not encourage initial therapy with dual agents in treatment-naïve patients who may otherwise be successfully treated with a single agent, and (c) the Division's desire to not lock patients into dual therapy, as some patients who start on dual therapy may be able to achieve excellent control with a single agent after the initial hyperglycemia is improved. Whether the data from the proposed study can be included in the Clinical Studies section of the label will be a review issue.

Sponsor Response: The Sponsor wishes to seek further clarification of this comment. The Sponsor is interested in understanding how the Division views the use of dapagliflozin in combination with metformin as initial or early combination treatment in newly diagnosed T2DM patients.

Meeting Discussion: The Division acknowledged that there are no safety concerns identified to date that preclude the proposed approach. However, the Division encouraged the Sponsor to delay evaluation of dapagliflozin in combination with metformin as an initial or early

treatment of newly diagnosed T2DM until the safety of dapagliflozin is established as monotherapy and as add-on to metformin. The Sponsor stated that there will be 5-6 months of safety data available at the time the Sponsor plans to begin the above study.

Question 7: Projected Total Clinical Exposures in the Dapagliflozin Phase 3 Program

Does the Agency agree that the proposed clinical exposure database to be submitted in the original NDA and 4-month safety update documenting the safety of dapagliflozin for the projected number of subjects treated and the projected distribution of patient exposure at 3 doses investigated at 6, 12, and 18 months, will be sufficient for registration of dapagliflozin for the treatment of hyperglycemia in adult subjects with T2DM?

Division Response: The Division agrees provided that no safety concerns arise. The Sponsor's estimated sample sizes should be available at the time of NDA submission. As explained above, one concern is whether long-term use of dapagliflozin may cause adverse effects on the kidney. Therefore, the Division strongly encourages representation of meaningful numbers of renal failure patients in your phase 3 program and recommend bolstering the numbers of patients who will have long term (>1 year) exposure to dapagliflozin at the time of NDA submission.

Sponsor Response: The Sponsor acknowledges the Division's comments and recommendations. The Sponsor intendeds to address this issue through labeling as well as stand-alone trial(s) that are separate from the proposed metabolic ward study. A planned PK/PD study in subjects with renal impairment is meant to address if dapagliflozin will retain comparable glucosuria and FPG change in subjects with impaired renal function as a complication of chronic T2DM. In addition, renal assessments in the proposed Phase 3 program should provide information to begin to address the renal safety of dapagliflozin in the T2DM population with normal and varying degrees of renal impairment (creatinine level up to 2 mg/dL or calculated creatinine clearance of down to 50 mL/min).

Because renal safety may be a primary concern of this class, the Sponsor wishes to seek additional clarification regarding the data that would be necessary from patients with normal renal function as well as patients with renal impairment for inclusion in the NDA. In particular, the Sponsor seeks clarification and would like to work with the Division to define the number of patients, the length of investigation, and the severity of renal disease that would be required for approval.

Meeting Discussion: See the Division's response to Question 4(a).

Question 8: Special Clinical Safety and MOA Studies

- a) BMS and AZ consider the MOA studies important to understand the MOA and provide physicians relevant information for use. Does the Agency have any comments on these 2 studies?

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[REDACTED] (b) (4)

- [REDACTED] (b) (4)

Division Response: The [REDACTED] (b) (4)

[REDACTED] **Division recommends that the Sponsor combine the two above studies into one metabolic balance study.** [REDACTED] (b) (4)

[REDACTED] **Because there may be potential adverse effects of long-term dapagliflozin use on the kidney, the Division requests the following modifications to the proposed metabolic balance study: (a) The Sponsor should include patients with mild, moderate, and severe renal impairment, (b) the Sponsor should bolster the number of patients in this study, and (c) the Sponsor should lengthen the duration of the study. The Division recommends that the Sponsor also obtain population PK data from this study.**

Sponsor Response: Please see the response to Question 7.

- b) Does the Agency have any additional comments regarding other MOA studies described below, which are under consideration to be conducted during ongoing dapagliflozin clinical development?
- A glucose titration study to examine the effects of dapagliflozin on the renal transport maximum for glucose (TmG) and the slope of the titration curve.
 - A study of the effects of dapagliflozin on albuminuria in subjects with diabetic kidney disease.
 - A euglycemic clamp study to evaluate the effect of dapagliflozin on glucose production and glucose utilization.

Division Response: The proposals seem acceptable.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

Question 9: Clinical Safety Monitoring Plans

- a) For the planned metabolic balance study does the Agency agree with the proposed approach to:
- monitoring alterations in renal function assessed as GFR in subjects receiving dapagliflozin;
 - assessing electrolyte and plasma volume homeostasis;
 - assessing the effects of dapagliflozin on urinary uric acid excretion, as well as the plan to monitor for potential consequences of increments in uricosuria?

Division Response: The proposal seems acceptable. Please see the Division's additional comments responding to Question 8a.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

- b) For the entire planned Phase 3 clinical program (all pivotal studies) does the Agency agree with the proposed approach to assessing the incidence of symptomatic urinary tract and genital infections?

Division Response: In addition to what the Sponsor proposes, the Sponsor should include a brief targeted questionnaire on the symptoms of genitourinary infections and perform directed questioning about these symptoms at clinic visits. For the entire Phase 3 program, the Sponsor should include standard analyses of the electrocardiogram data (e.g., QT, QTcB, QTcF ≥ 500 msec, >30 msec change from baseline, >60 msec change from baseline, etc).

Sponsor Response: The Sponsor acknowledges the Division's recommendation, and wishes to confirm that events of GU tract infections will be captured on specialized case report forms along with additional information on the events. With regard to the proposal to include standard analyses of the ECG, the Sponsor would like to understand the Division's view on any need for further ECG and QTc evaluation in light of current data and the dedicated ECG clinical pharmacology study; please also see response to comments on Question 2c.

- c) For the monotherapy and combination with metformin studies, including both short-term and long-term extension phases of these studies does the Agency agree with the plans to monitor changes in bone turnover markers, whole-body bone mineral content, and bone mineral density?

Division Response: The proposal seems acceptable. However, the Division recommends that the Sponsor also measure 25 hydroxy-vitamin D concentrations, because levels of this hormone could affect the serum PTH and serum calcium concentrations.

Sponsor Response: The Sponsor concurs with the Division's recommendations, and no further discussion is requested.

Question 10: Pediatric Studies

BMS and AZ recognize that the combined benefits of glycemic control and weight reduction could make dapagliflozin a valuable therapeutic option in adolescents with T2DM. However, currently no information is known regarding the safety, tolerability, and efficacy of dapagliflozin in patients with T2DM less than 18 years of age. Additionally, there is very little prevalence of T2DM in children less than 10 years of age.

- a) Does the Agency agree to grant a waiver for the study of dapagliflozin in pediatric subjects of the age range in which T2DM is rare (< 10 years of age)?

- b) Does the Agency agree that initiation of safety and efficacy studies in adolescent patients with T2DM (> 10 years to < 18 years) may be deferred until completion of the Phase 3 program and submission of the NDA?

Division Response: The proposal seems acceptable. The Sponsor should submit a formal request at the time of NDA submission. The Division reminds the Sponsor that the pediatric development program will require addressing the safety and efficacy of smaller doses of dapagliflozin. Therefore, the proactive approach to dose selection (see response to Question 3a) will serve the clinical development of dapagliflozin in children as well as in adults.

Sponsor Response: *The Sponsor acknowledges the Division's response, and intends to communicate with the Division regarding the investigation of T2DM pediatric patients, in accordance with the Best Pharmaceuticals for Children Act. With regard to addressing the safety and efficacy, as stated in Question 3a, the Sponsor will discuss the need for substantiation of efficacy and tolerability of doses lower than 2.5 mg.*

Question 11: [REDACTED] (b) (4)

It is expected that the loss of glucose induced by dapagliflozin may result in significant ongoing negative caloric balance. This expectation is supported by the reduction in body weight observed in the Phase 2B study. All Phase 3 studies will measure the change from baseline in total body weight in a consistent manner as a secondary endpoint, considering the clinical relevance of weight loss in patients with T2DM treated with dapagliflozin.

Does the Agency agree that the proposed approach will support inclusion of the following data in the Clinical Studies section of the dapagliflozin label [REDACTED] (b) (4)

[REDACTED] based upon both monotherapy and combination therapy trials with placebo arms?

- Mean weight change from baseline in weight measure and percentage
- A1C [REDACTED] (b) (4)

Division Response: This is a review issue. For an indication to control hyperglycemia in type 2 diabetes, we may allow the inclusion of controlled data on weight change in the Clinical Studies section of the label. [REDACTED] (b) (4)

Sponsor Response: *The Sponsor acknowledges the Division's comments. The Sponsor wishes to confirm that their intention is to provide weight-related information in the context of diabetes, in order to inform physicians of this clinically relevant data.* [REDACTED] (b) (4)

ATTACHMENT:

Slides presented by Sponsor during the meeting

Minutes Preparer: Julie Marchick

Chair Concurrence: Mary Parks

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/s/

Julie Marchick
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