

Hartford, Rachel

From: Hartford, Rachel
nt: Monday, June 22, 2009 1:46 PM
o: 'Smith, Pamela'
Subject: FW: saxagliptin

Pam.

We have reviewed the clarification below and are still unclear.

It is stated that 80 patients in Study -039 and 22 patients in Study -038 had a frozen A1c sample used in the calculation of change from baseline to Week 24 (LOCF). This seems to be at odds with the statement below that only 8 patients were excluded from -039 and no patients were excluded from -038 for calculating the change from baseline in HbA1c.

Are you stating in the last paragraph that frozen A1c samples from these 102 patients would be classified as "missing" for calculating the primary efficacy endpoint of change from baseline in HbA1c?

Rachel

From: Smith, Pamela [mailto:pamela.smith@bms.com]
Sent: Tuesday, June 09, 2009 12:13 AM
To: Hartford, Rachel
Subject: RE: saxagliptin

Dear Rachel,

Please see below for our clarification Response regarding your query regarding the number patients/samples used in the calculation of the primary endpoint in the studies in which patients from Russia were enrolled and for which samples were en:

Appendix 1.1 and Appendix 2.1 of the response to Question 2 of May 11 reports the number of subjects with at least one sample that was frozen as a result of the Russian export suspension and subsequently used in the calculation of change from baseline to Week 24 (LOCF). A total of 80 subjects from study CV181039 had at least one frozen sample and 22 subjects from study CV181038 had at least one frozen sample.

Tables 1 and 2 of the response to Question 3 of May 11 reports the change from baseline in A1C including all data (top panel) and excluding data from the frozen samples (bottom panel) to illustrate the impact on excluding the frozen samples. The number of subjects data that were totally excluded from the analysis of A1C change from baseline due to the exclusion of the frozen samples was 8 from study CV181039, and no subject data were totally excluded from study CV181038. The analysis of A1C change from baseline (LOCF) excluding the frozen samples applied the same rules as in the Clinical Study Reports, ie, the last value prior to Week 24, prior to rescue, was used. Thus, the majority of subjects who had at least one frozen sample had A1C data from other (non frozen) samples that were used in the LOCF analysis.

I hope this is helpful. Please let me know if we should formally submit this clarification response to the NDA.

Thanks,

Pam

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Thursday, June 04, 2009 5:27 PM
To: Smith, Pamela
Subject: RE: saxagliptin

6/29/2009

Good Afternoon Pam,

Please clarify the "n" in Tables 1 and 2 under Response 3. These "n" do not appear consistent with the Response to question 1 where it states that 80 patients in CV181039 had a frozen A1c sample used in the calculation of the primary endpoint and that patients in CV181038 had a frozen A1c sample used in the calculation of the primary endpoint.

Thank you,

Rachel

From: Smith, Pamela [mailto:pamela.smith@bms.com]

Sent: Tuesday, June 02, 2009 10:25 AM

To: Hartford, Rachel

Subject: RE: saxagliptin

Hi Rachel,

Attached please find Responses to Question 1, 2, and 3 of the May 11 query about lab samples involved in the suspension of shipment of samples from Russia. We will formally submit the Responses to all 3 questions this week.

Pam

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]

Sent: Monday, May 11, 2009 9:40 AM

To: Smith, Pamela

Subject: saxagliptin

Good Morning Pam,

We have a few additional information requests regarding the suspension of samples from Russia:

1. Is there evidence to show that the freezing and thawing of samples did not affect reliability of the data?
2. How many samples (total and by study) used for the efficacy analyses were affected as a result of the suspension?
3. If the affected samples were excluded, would the efficacy results be consistent?

Thanks,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, June 04, 2009 5:30 PM
To: 'Smith, Pamela'
Subject: Lymphocyte request

Hello again,

Please conduct the following subgroup analyses on the phase 2/3 data for lymphocyte counts (mean changes, shifts, outliers):

1. Patients on strong CYP3A4 inhibitors (e.g., Ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin)
2. Patients on moderate CYP3A4 inhibitors (e.g., Diltiazem, aprepitant, erythromycin, fluconazole, fosamprenavir, verapamil, amprenavir)
3. Asians

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
nt: Thursday, June 04, 2009 5:27 PM
o: 'Smith, Pamela'
Subject: RE: saxagliptin

Good Afternoon Pam,

Please clarify the "n" in Tables 1 and 2 under Response 3. These "n" do not appear consistent with the Response to question 1, where it states that 80 patients in CV181039 had a frozen A1c sample used in the calculation of the primary endpoint and that 22 patients in CV181038 had a frozen A1c sample used in the calculation of the primary endpoint.

Thank you,

Rachel

From: Smith, Pamela [mailto:pamela.smith@bms.com]
Sent: Tuesday, June 02, 2009 10:25 AM
To: Hartford, Rachel
Subject: RE: saxagliptin

Hi Rachel,

Attached please find Responses to Question 1, 2, and 3 of the May 11 query about lab samples involved in the suspension of shipment of samples from Russia. We will formally submit the Responses to all 3 questions this week.

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Monday, May 11, 2009 9:40 AM
To: Smith, Pamela
Subject: saxagliptin

Good Morning Pam,

We have a few additional information requests regarding the suspension of samples from Russia:

1. Is there evidence to show that the freezing and thawing of samples did not affect reliability of the data?
2. How many samples (total and by study) used for the efficacy analyses were affected as a result of the suspension?
3. If the affected samples were excluded, would the efficacy results be consistent?

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)

6/29/2009

saxagliptin

301-796-9712 (fax)

Page 2 of 2

6/29/2009

**PreApproval Safety Conference
Overview of Meeting**

MEETING DATE: June 2, 2009

TIME: 8:00 – 9:30am

LOCATION: FDA - Federal Research Facility
White Oak Building 22, Rm 3270
10903 New Hampshire Avenue
Silver Spring, MD

APPLICATION: NDA 22-350 Onglyza (saxagliptin) tablet

ATTENDEES (alphabetic): (Title and Office/Division)

Fred Alavi, Ph.D.
Pharmacology/Toxicology Reviewer, Division of Metabolism and Endocrinology Products
(DMEP)

Ali Al Hakim, Ph.D.
Chief, Division of Pre-Marketing Assessment I (DPA-I)

Lina Aljuburi, Pharm.D.
Chief, Project Management Staff, DMEP

Todd Bourcier, Ph.D.
Supervisor, Pharmacology/Toxicology, DMEP

Jessica Diaz, RN, BSN
Patient Product Information Reviewer, Division of Risk Management

Amy Egan, M.D.
Deputy Director for Safety, DMEP

Rachel Hartford
Regulatory Project Manager, DMEP

John Hill, Ph.D.
Chemistry Reviewer, DPA-I

Hylton Joffe, M.D., M.M.Sc.
Clinical Diabetes Team Leader, DMEP

ADDITIONAL ITEMS:

1. Status of Labeling Reviews
 - a. PLR format review – complete
 - b. High-level DRISK review – complete
 - c. DDMAC initial review – complete
 - d. DMEPA initial review – complete
 - e. CMC initial review – complete

2. DSI Inspection: Clinical Inspection Summary – complete

3. Sign-off procedure and schedule
 - a. Action Package due to the Division Director – 22Jun09
 - b. Action Package due to the Immediate Office – 9Jul09
 - c. Action Letter due to SRT – 13Jul09
 - d. PDUFA goal date – 31Jul09

Supervisory Concurrence:
Lina Aljuburi
Chief, Project Management Staff

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

RACHEL E HARTFORD
07/30/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, May 12, 2009 1:37 PM
To: 'Smith, Pamela'
Subject: Request

Hello Pam,

We have an additional request:

Provide an analysis of pancreatitis cases occurring with saxagliptin and comparators in your controlled phase 2/3 clinical trials. Present data by individual study and for the placebo-controlled pooled safety populations. Include a description of how events were identified.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

Rachel E Hartford
5/12/2009 01:39:37 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, May 11, 2009 9:40 AM
To: 'Smith, Pamela'
Subject: saxagliptin

Good Morning Pam,

We have a few additional information requests regarding the suspension of samples from Russia:

- 1. Is there evidence to show that the freezing and thawing of samples did not affect reliability of the data?**
- 2. How many samples (total and by study) used for the efficacy analyses were affected as a result of the suspension?**
- 3. If the affected samples were excluded, would the efficacy results be consistent?**

Thanks,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

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/s/

Rachel E Hartford
5/11/2009 02:38:37 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-350

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your June 30, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onglyza (saxagliptin) tablet, 2.5 mg and 5 mg.

On April 15, 2009, we received your April 15, 2009, amendment to this application. This submission contains BMS study report DN08072: Saxagliptin (BMS-477118) and Metformin (BMS-207150): Oral Combination Study of Embryo-Fetal Development in Rats. This is a major amendment. 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 **July 30, 2009**.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at 301-796-0331.

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/

Mary Parks
4/20/2009 11:50:43 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD, 20857

IND 63,634
c
NDA 22-350

3/25/09

b(4)

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

Dear Dr. Smith:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for saxagliptin tablet and saxagliptin/metformin XR fixed-dose combination tablets and your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for saxagliptin tablet, 2.5 mg and 5 mg.

We also refer to your amendments to INDs 63,634 c) dated March 6, 2009, containing a 15 day non-clinical safety report. The safety report contains information regarding results of neural tube defects and other malformations in rats during the embryofetal development study.

b(4)

We do not agree that the current data are sufficient to exclude a potential interaction of the saxagliptin/metformin combination in causing the teratogenic effect observed in this study. We therefore request that you take the following actions:

1. Submit the full report of the rat embryofetal development study with the saxagliptin/metformin combination along with relevant historical incidence data as soon as it becomes available.
2. Repeat the rat embryofetal development study with a design that includes separate arms for metformin alone, saxagliptin alone, and the combination of saxagliptin + metformin. We also ask that you conduct an embryofetal development study in rabbits with a similar study design.

3. Because saxagliptin would be commonly used in conjunction with metformin if it receives marketing approval, propose language that discloses the teratogenic finding in the marketing label for saxagliptin (NDA 22-350).

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

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/

Todd Bourcier
3/25/2009 01:09:39 PM
Signing for Dr. Parks

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, March 18, 2009 2:01 PM
To: 'Smith, Pamela'
Subject: Saxagliptin statistical request

Hello Pam,

The interpretation of the cardiovascular events is dependent on the observed confidence intervals. In turn, the size of the confidence interval is dependent on the statistical method used. For example, in your response to the FDA January 2009 request, you computed an incidence rate ratio of 0.48 with 95% confidence interval of 0.24 to 0.96 for Custom MACE (ST+LT); in your briefing document, you present an incidence rate ratio of 0.48 with 95% confidence interval of 0.25 to 0.90. Clearly the interpretation of these results do not differ. However it is important to us to understand precisely the methods that led to the differing intervals.

Please provide us with the name of the software packages you used and an example of the coding you used for the following methods:

- Cox proportional hazards model for computing the overall stratified risk ratio
- Exact procedure for computing the overall stratified risk ratio
- Exact procedure for Poisson processes for computing the overall stratified incidence rate ratio
- Mantel-Haenszel method for computing the overall stratified incidence rate ratio
- Mantel-Haenszel method for computing the overall stratified risk difference

We have applied some of these methods in our analyses of the CV data and so this information will help us in comparing our programs to yours.

Please provide a response timeframe.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, March 18, 2009 3:13 PM
To: 'Smith, Pamela'
Subject: Integrated Summary of Safety Appendix request

Good Afternoon Pam,

Please see our request below and provide a response as soon as possible.

Certain laboratory analyses could not be located in the Integrated Summary of Safety Appendix. For the pooled monotherapy studies:

1. Please provide the location of the following labs (expressed as change from baseline to endpoint) : basophils (%), eosinophils (%), erythrocytes (%), hematocrit, hemoglobin, lymphocytes (%), monocytes (%), leukocytes (%), neutrophils (%), direct bilirubin, BUN, chloride, potassium, sodium, uric acid, and urinalysis (creatinine, microalbumin, microalb/creatinine ratio, pH, SG). If these have not been provided, please do so for the pooled monotherapy population only.

2. In addition, please provide the location for shift tables for the following labs for the pooled monotherapy studies: hemoglobin, hematocrit, WBCs, sodium, potassium, creatinine (please provide if not submitted).

Thank you,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, March 13, 2009 9:10 AM
To: 'Smith, Pamela'
Subject: RE: One more CMC Clarification

Pam,

The wording below is acceptable.

Thanks,

Rachel

From: Smith, Pamela [mailto:pamela.smith@bms.com]
Sent: Thursday, March 12, 2009 4:02 PM
To: Hartford, Rachel
Subject: One more CMC Clarification

Dear Rachel,

Just one (hopefully) last CMC clarification, re spelling, capitalization, etc. Please see below for the exact proposed wording to confirm acceptability:

Each tablet contains 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin.

Each tablet contains 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin.

Thanks in advance,

Pam

3/13/2009

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, March 12, 2009 8:49 AM
To: 'Smith, Pamela'
Subject: RE: CMC Clarification

Pam,

We found the alternative proposal acceptable. Sorry for the confusion. Thus the labeling will read:

Each tablet contains 2.79 mg saxagliptin HCl (anhydrous) equivalent to 2.5 mg saxagliptin,
or
Each tablet contains 5.58 mg saxagliptin HCl (anhydrous) equivalent to 5 mg saxagliptin

Thanks,

Rachel

From: Smith, Pamela [mailto:pamela.smith@bms.com]
Sent: Wednesday, March 11, 2009 10:12 PM
To: Hartford, Rachel
Subject: CMC Clarification

Dear Rachel,

Per our conversation, here is the CMC item for which we would like clarification. Please see below.
ks,

Pam

PS: I also have a followup question about the Tradename approval letter. I will call you on Thursday.

Clarification Request:

The Agency indicated that our response to Question 12 of the December 11 FDA CMC questions was acceptable. However, we repeated our original proposal as our preferred option:

(1)

Each tablet contains 2.5 mg saxagliptin (as saxagliptin hydrochloride),
or
Each tablet contains 5 mg saxagliptin (as saxagliptin hydrochloride)

And we also proposed this alternative if the original proposed wording was not acceptable:

(2)



b(4)

Our preference would be to use the originally proposed language:

(1)

3/12/2009

Each tablet contains 2.5 mg saxagliptin (as saxagliptin hydrochloride),
or
Each tablet contains 5 mg saxagliptin (as saxagliptin hydrochloride)

Does the Agency agree that this will be acceptable?



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,634
NDA 22-350

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

3/11/09

Dear Dr. Smith:

Please refer to your Investigational New Drug application (IND) submitted under 505(i) of the Federal Food, Drug, and Cosmetic Act and your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for saxagliptin tablet, 2.5 mg and 5 mg.

We also refer to your May 30, 2008, correspondence to IND 63,634, received June 2, 2008, requesting review of the proposed proprietary name, Onglyza. This proposed proprietary name also applies to NDA 22-350, submitted and received on June 30, 2008.

We have completed our review of **Onglyza** and have concluded that it is acceptable.

Onglyza 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 May 30, 2008, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

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/

Mary Parks
3/11/2009 11:27:38 AM

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, March 09, 2009 9:18 AM
To: 'pamela.smith@bms.com'
Subject: Label Comments

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

The Division of Medication Error Prevention and Analysis developed the following label comments.

1. 2.5 mg; 30 and 90 Count Container Label

Revise the prominence of the established name to ensure that it is ½ the size of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10 (g)(2) which will improve the prominence of the established name.

2. Sample Blister Folder Label and Sample Tray

- a. Relocate the dosage form and strength to be in accordance with CFR 21 CFR 201.57(a)(2) so that it is not located between the proposed proprietary name and the established name. We also recommend increasing the prominence of the 5 mg per tablet statement by increasing the size and font on the primary display panel. This will increase the visibility of the strength and dosage form and make this pertinent information more readily accessible to practitioners.
- b. The dosage form should directly follow the established name, i.e. Saxagliptin Tablets.
- c. Improve the readability of the proprietary name, Onglyza, by removing the lighter font on the middle letters, gly. We recommend replicating the presentation of the name on the trade container label.
- d. Delete the numbered days on the blister folder as they are presented in a nonintuitive manner (i.e., vertical rather than horizontal). The tablets in this packaging configuration do not have to be taken in a specific order and thus do not require the numbered days of the week which may be confusing to the patients.

Regards,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, March 09, 2009 6:47 AM
To: 'pamela.smith@bms.com'
Subject: Feedback on the CMC Reponses

Follow Up Flag: Follow up
Flag Status: Purple

Good Morning Pam,

We have evaluated your dissolution testing proposal (February 26, 2009) submitted in response to CMC deficiency #5 (December 11, 2008). We cannot accept your proposal in light of the 21 CFR 211.165 requirement that **each** batch of drug product be evaluated for conformance to specifications. Include dissolution testing as part of routing lot release and stability testing for all strengths of the saxagliptin drug product.

Your responses to the other CMC deficiencies communicated in the December 11, 2008 letter have been evaluated and deemed to be adequate.

We recognize that there could be possible alternative approaches to ensure bioavailability of the drug product. We would be willing to discuss alternative approaches to dissolution testing. Because of the review timelines, such discussion may be more appropriate post-approval.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, March 06, 2009 12:09 PM
To: 'pamela.smith@bms.com'
Subject: Location Request

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

We have the following request and would like a response today if possible:

Please specify the location of the dataset for subjects with MAs of lymphocytes (should include Day of event).

Thank You,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, February 05, 2009 2:59 PM
To: 'pamela.smith@bms.com'
Cc: 'joseph.lamendola@bms.com'; Patrice E Todd
Subject: CMC Request

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

We have an additional CMC request. Please provide COA's (including specifications for specific activity) for ϵ and δ in the planned February 20, 2009 CMC response.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

b(4)

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, January 30, 2009 2:27 PM
To: 'pamela.smith@bms.com'
Subject: Baseline Comorbidity Information Question

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

One more question:

Aside from the baseline demographic and diabetes characteristics provided in the Appendix to the Summary of Clinical Safety, where can baseline comorbidity information (hypertension, CAD, dyslipidemia, etc.) be found?

Hope you have a great weekend,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, January 28, 2009 1:26 PM
To: 'pamela.smith@bms.com'
Cc: 'joseph.lamendola@bms.com'; Patrice E Todd
Subject: Saxagliptin MACE request

Follow Up Flag: Follow up
Flag Status: Purple

Hello Pam,

Please respond to the following ASAP:

1. It appears that terms that were not listed as "Custom MACE" terms by the Division were used in your Custom MACE analysis. Examples include "pulmonary embolism " and "cardiac failure congestive". Please clarify this apparent discrepancy.

2. Provide narratives for the following subjects with the PT "infarction": 181039-199-581, 181040-39-1735, 181013-231-335.

Thanks,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, January 15, 2009 10:29 AM
To: 'pamela.smith@bms.com'
Subject: NDA 22-350 Information Request

Follow Up Flag: Follow up
Flag Status: Purple

Good Morning Pam,

I have a Clinical Pharmacology question for you. Were any drug interaction studies of saxagliptin with rifampin and oral contraceptive conducted? If so, please submit the study reports to the NDA.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, January 13, 2009 12:01 PM
To: 'pamela.smith@bms.com'
Cc: Aljuburi, Lina
Subject: RE: Clarification Request
Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Our responses to your clarification requests are inserted into the text of your email below (Bold Blue).

Sincerely,

Rachel

From: pamela.smith@bms.com [mailto:pamela.smith@bms.com]
Sent: Monday, January 12, 2009 11:01 PM
To: Hartford, Rachel; Aljuburi, Lina
Subject: Clarification Request

Dear Rachel
(and Lina)

Per my telephone conversation Monday evening January 12 with Lina, please see below for our urgent request for clarification of two items in the Information Request Letter issued by the Agency January 11, 2009 for Saxagliptin NDA 22-350. We hope these queries can be quickly clarified so that we can complete and submit our responses by January 21, as requested in the Agency's letter. We are available for a teleconference on Tuesday if needed.

Thanks very much to both of you for your assistance,

Pam

Question IB Re the "additional analysis population": The Sponsor proposes to provide analyses using the 120-day safety update database, as this version is the most complete and up-to-date version of the saxagliptin data that has been submitted to the FDA for its review of the NDA. Does the Agency agree?

Yes, the additional analysis should use the 120-safety update database. Please note that the analysis of the short-term period should exclude data from patients after initiation of rescue (these patients move directly into the long-term extension and their additional data should be included in the second analysis (I.B.)).

Question II. Re MACE events to be included in the analysis: The sponsor acknowledges the FDA request (e-mail correspondence, December 19, 2008) to "resubmit the table of MACE events incorporating these subjects:

- CV181011-10-459: narrative uses the term "acute coronary syndrome"
- CV181038-87-811: narrative describes discharge diagnosis "extensive AW STEMI"

Sponsor also acknowledges the FDA request (letter issued January 9, 2009)
or nonfatal events, use MedDRA Preferred Terms as they were originally assigned in the NDA submission" and to
"...not use post hoc adjudication for nonfatal events."

The sponsor proposes, in accordance with the FDA recommendation (December 19 email) that subject CV181038-

3/9/2009

878-811 should be designated as having had a MACE event and should be included in the MACE analysis requested January 11, 2009

Additionally, the Sponsor proposes that the AE for subject CV181011-10-459 ("Chest Pain and ECG abnormalities") does not qualify as a MACE event and should not be included in the analysis requested in the letter issued January 11, 2009 for the following reasons: The narrative reflects the fact that the investigator clearly documented his amended opinion that the event did not represent an "acute coronary syndrome". In response to this question he further provided to BMS the medical record documents which were available at the site supporting his conclusion. This evidence suggests there was no myocardial injury by enzymes, or ECG criteria. There is also no evidence clinically of anything more than transient ischemia (reversible in an adenosine study). The final PTs for this subject were Chest Pain and Coronary Artery Disease. Medical review by the Sponsor supports the conclusion of the investigator that the diagnosis of "acute coronary syndrome" is not consistent with the available data.

The Sponsor proposes that this event *NOT* be considered a MACE event and *NOT* be included in the requested MACE analysis since the PTs of Chest Pain and Coronary Artery Disease (which we believe accurately represent the event) are not in any of the MACE lists.

(Narratives and Key updated information from the medical record will be provided in the response to the December 19, 2008 request for information)

Lastly, the sponsor wishes to point out that the standardized MedDRA query for "Myocardial Infarction" includes the preferred term "Blood Creatine Phosphokinase Increased". In our experience, this term is typically applied to events that are not MI-related due to its non-specificity and is, additionally, relatively common. As an example, there were 38 subjects who were reported to have an AE with this PT in an analysis of our pooled population of 5 Phase 3 placebo-controlled studies up to Week 24 including rescue, alone. As a consequence, we have not typically included this term in our MACE analyses due to its non-specificity and its potential to conceal a true cardiovascular signal. Does the FDA prefer to maintain this PT in the SMQ MACE endpoint?

You should treat the January 11, 2009 information request (IR) separately from the December 19, 2008 IR. Specifically, if you have issues from the December request regarding reclassification of certain subjects with MACE events, this should be addressed in the response to that request with sufficient explanation. The explanation of why subject's CV181011-10-459 event does not represent MACE should be included in that submission. For the response to the January letter, you should adhere to the IR's content that post-hoc adjudication should not be used.

With regard to the "increased CPK" question, please include the terms as specified in the request. Note that the listing requested will delineate all events experienced by each patient and that FDA review and interpretation of the results will consider the totality of the data.

<!--[if !supportAnnotations]-->

<!--[endif]-->

<!--[if !supportAnnotations]-->

<!--[endif]--><!--[if !supportAnnotations]--><!--[endif]-->

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

/s/

Rachel E Hartford
3/17/2009 03:04:28 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-350

INFORMATION REQUEST LETTER

Bristol-Myers Squibb Company
Attention: Pamela J. Smith, M.D.
Group Director, GRS
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. McElligott:

Please refer to your June 30, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for saxagliptin tablets.

In anticipation of the upcoming Advisory Committee meeting for your product, we request that you submit for our review the following data regarding major adverse cardiovascular events (MACE).

Submit the requested data no later than January 21, 2009, to ensure that there is sufficient time for review.

Please provide information and analyses regarding MACE events as follows:

I. Analysis population(s):

A. The main analysis population should include the randomized, double-blind, controlled short-term periods for all completed Phase 2 and Phase 3 trials of your product.

B. An additional analysis population should include the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of your product. That is, include unblinded periods if they remain controlled, and include controlled data past the primary HbA1c efficacy measurement, if applicable. Do not include uncontrolled extension periods.

II. Endpoints: Use the following two endpoints, which will be referred to hereafter as "SMQ MACE" and "Custom MACE". We acknowledge that there may be many opinions about what precise terms should be included in these endpoints, but these are the terms we want you to use. For nonfatal events, use MedDRA Preferred Terms as they were originally assigned in your NDA submission. Do not use post hoc adjudication for nonfatal events. Adjudication of cardiovascular deaths is acceptable. Do not add or subtract Preferred Terms from either endpoint. If you wish to provide separate analyses with independent external post hoc

adjudication of nonfatal events from the specified endpoints, you may do so, but you must submit the analyses with unadjudicated Preferred Terms for nonfatal events as requested.

“SMQ MACE”: Use a composite endpoint of cardiovascular death, and all Preferred Terms in the Standardised MedDRA Queries for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents”.

“Custom MACE”: Use a composite endpoint of cardiovascular death and the following MedDRA Preferred Terms:

- Acute myocardial infarction
- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Coronary artery thrombosis
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Postprocedural stroke
- Silent myocardial infarction
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

III. Types of Analyses

A. Listing

List all events (including those from uncontrolled portions of the trials) from both the “SMQ MACE” and the “Custom MACE” endpoints, including both the first event observed and any subsequent events observed. The listing should be sorted by treatment group and patient ID. For patients with multiple events, the events should be listed in order of occurrence. The events should be defined by MedDRA Preferred Terms. A proposed format for this listing is shown below:

Table 1 (example) Listing of MACE events sorted by treatment group and type of event for all studies

Pt ID	Study	Treatment	MedDRA Preferred Term	Date of event	Time on study at time of event	In the main analysis population?	Serious event?	SMQ MACE?	Custom MACE?

B. Summaries

1. Summary of the incidence of SMQ MACE and Custom MACE events in the main analysis population and in the additional analysis populations by dose of the study drug. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 2 (example) Incidence of SMQ MACE events in the main analysis population, by dose of study drug

	Dose 1	Dose 2	Dose 3	All Doses	Placebo Comparator	Active Comparator
Pooled	x/X (y%)					
Study 1						
Study 2						
Study 3						
Study 4						

x= number of events for that group

X=total number of randomized patients in the safety database for that group

y=x/X times 100

2. Summaries of the incidence of SMQ MACE events and Custom MACE events in the main analysis population and the additional analysis population, combined across doses of the study drug in separate tables. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE events and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 3 (example) Incidence of SMQ MACE events in the main analysis population, combined across doses of study drug, reported separately by study

Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (events/N)	Incidence ratio, 95% CI	Incidence difference, 95% CI	Incidence rate (events/Pt -yrs)	Incidence rate ratio, 95% CI	Incidence rate difference, 95% CI
Study 1	Study Drug									
	Active Comparator									
	Placebo Comparator									
Study 2	Study Drug									
	Active Comparator									
	Placebo Comparator									
etc	etc									
etc	etc									
Overall results stratified by study										

C. Analyses

For SMQ MACE and custom MACE, analyze both the incidence (events/N) and the incidence rate (events/patient-year) using the analysis populations described under I. A. and B. of this document. If the set of Phase 2 and 3 studies has more than one type of comparator group, we recommend making two comparisons: a) the study drug compared to the placebo; and b) the study drug compared to the placebo and the active comparator groups combined. Analysis b) is the analysis that should be presented in the last line of Table 3 and the Forest plots discussed in Section D.

The analyses should be stratified by study and we recommend that a stratified exact method be included as one of the analyses. However, we acknowledge that multiple studies may have 0

MACE events in one or more groups and that pooling studies for an unstratified analysis may be a reasonable alternative.

D. Forest Plots

For SMQ MACE and custom MACE, provide a forest plot depicting the incidence ratio results from the individual studies and the results from the overall stratified analysis for the primary analysis population described in I. A.

E. Electronic Data Files

Please provide a dataset with a single observation for each patient which includes the following:

- Study identifier
- Unique patient identifier
- Demographic data
- Date of randomization
- Treatment group
- Date of completion/rescue/discontinuation of the randomized, controlled, double-blind period of the study
- Exposure time in the randomized, controlled, double-blind period of the study
- Participated in extension study (Yes/No)
- For each of the composite endpoints ("SMQ MACE" and "Custom MACE"), include the following set of variables:
 - a) Duration of time from randomization to date of first event or censoring
 - b) Indicator for whether or not the event took place during the short-term period or long-term extension
 - c) Censoring variable
 - d) Date of event or censoring
- MedDRA Preferred Term for "SMQ MACE"
- MedDRA Preferred Term for "Custom MACE"

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at 301-796-0331.

Sincerely,

{See appended electronic signature page}

Mary 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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this page is the manifestation of the electronic signature.**

/s/

Hylton Joffe
1/11/2009 01:30:10 PM
Hylton Joffe for Mary Parks

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, January 07, 2009 1:18 PM
To: 'pamela.smith@bms.com'
Subject: Clarification Request

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Thank you for quickly clarifying the passage below. The strike-out font feature was applied to the initial values and the corrected value are in red font. Please verify that the passage below is correct. Instead of requesting a submission, I will add your email verification as documentation to our file.

From page 232 Summary of Clinical Safety included in the original NDA submission:

In Table 3.1M, among the 30 subjects with non-isolated declines in absolute lymphocyte count, approximately one-half (16) (~~14~~) were associated with an infection-related AE and approximately one-half (14) (~~16~~) were not associated with an infection-related AE at any time during the ST+LT period. Five (5) of these 16 subjects with an infection-related AEs did not appear to have any temporal relationship with low lymphocyte counts, as these AEs either substantially preceded or were reported substantially later than dates reported for low lymphocyte count. Among the 16 subjects that had infection-related AEs presented in Table 3.1M, 11 were associated with some temporal relationship (within 30 days of the MA value or other values < LLN as noted in the comment column of Table 3.1M). Of these 11 subjects, all had a baseline absolute lymphocyte count < LLN or in the low-normal range at baseline. Specifically, 5 subjects had an absolute lymphocyte count < LLN; 6 subjects had an absolute lymphocyte count of 1.0-1.99 x 10³ c/ μ L). All of these subjects continued to have an absolute lymphocyte count < LLN or minimally above the LLN and generally maintained values for absolute lymphocyte count in this low range throughout the course of the studies. As noted above, it was not unexpected that these subjects had an infection that was temporally associated with a low absolute lymphocyte count as these subjects persistently had laboratory values in that range; therefore, any infection would be temporally associated with a low absolute lymphocyte count. A

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

Rachel E Hartford
3/17/2009 03:06:47 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
nt: Monday, December 29, 2008 2:28 PM
o: 'pamela.smith@bms.com'
Subject: FW: Clinical IR for saxagliptin NDA 22-350
Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Here are our responses to your 23 Dec 08 request for clarification:

Question 1: Please provide the requested analysis to include events for both 1) ST and 2) ST + LT

Question 3: Yes, provide the MACE analysis to include the ST, excluding rescue.

Question 5: Yes.

Question 6: Yes.

Thanks,

Rachel

From: pamela.smith@bms.com [mailto:pamela.smith@bms.com]
Sent: Monday, December 29, 2008 2:04 PM
Hartford, Rachel
ject: Re: Clinical IR for saxagliptin NDA 22-350

Rachel,

Please see below for a response to your query:

Pam

I can be reached at () (cell) and I am able to check email at least once daily. **b(6)**

Explanation of ST and Wk 24 Analyses in SCS:

The terms "ST period" and "up to Week 24" are not used interchangeably. Two distinct, complementary analyses were used to evaluate data collected through Week 24 in both the SCS and in the clinical study reports, as follows.

Approach 1) ST Analyses (ST period, excluding rescue)

Approach 1 (ST period, excluding rescue) was predicated on including subject data up to one of the following timepoints: (a) the final ST study visit (nominal visit date at Wk 24) or; (b) time of rescue in ST (subjects transitioned to the LT phase upon rescue); or (c) discontinuation of study drug. Here, if a subject were rescued, they entered the next study phase (i.e., the LT period); data collected after the subject entered this phase were not included in AE tables using this Approach.

Pre-specified conventions were defined for explicitly determining AEs to be counted in summary tables. AEs that were not SAEs were counted in summary tables if their onset date occurred on or up to 1 day after the last dose of study medication or last vital sign visit date whichever occurred last (or up to the start of the next study phase (if appropriate),

3/9/2009

whichever comes first). SAEs were counted if their onset date occurred on or up to 30 days after the last dose of study medication. (See SAP - Core Statistical Analysis Plan and SAP - Summary of Clinical Safety and Integrated Summary of Safety).

While the nominal last visit date for ST was at Wk 24, the P3 protocols permitted visits to occur in a window around the target visit date (+/- 3 days). Thus some subjects had final ST visit dates that occurred before or after the nominal Wk 24 date. Subjects assigned to saxagliptin treatment groups had, in general, a longer mean duration of follow up in the ST analyses excluding rescue than did subjects assigned to the control group. This occurred, in large part, because saxagliptin improved glycemic control in the Phase 3 studies, and subjects who received saxagliptin required less rescue for lack of glycemic control than did subjects who received placebo. The ST analyses formed the basis for assessing safety in the ST CSRs and was used in many presentations of safety in the SCS.

Approach 2) Wk 24 Analyses (Up to Week 24, regardless of rescue status):

As noted above, the mean duration of follow up in the ST analyses was longer for subjects randomized to saxagliptin treatment groups compared to subjects randomized to the control group. To address this asymmetry in duration of follow up, additional safety analyses were performed based on truncating the experience of each subject at Wk 24 (i.e., Day 169), regardless of rescue. Thus the Wk 24 analyses included some experience that occurred after rescue and occurred in the LT period (if rescue therapy was administered prior to Day 169) and excluded some experience that occurred prior to the final ST visit (if the final ST visit occurred after Day 169)."

As an example, Table 2.3.7A presents analyses based on both Approaches, as designated in the headers of the table. Analyses of the pooled monotherapy and add-on combination studies are based on data from the ST period, excluding rescue (Approach 1). Analyses of the placebo-controlled pooled safety population are based on data up to week 24, excluding rescue (Approach 2).

Hartford, Rachel wrote:

Joe and Patrice

Before we respond to the clarification requests, please reply to the questions below. It will help us answer your questions.

Are the terms "ST period" and "up to Week 24" being used interchangeably (as in Table 2.3.7.A)? If not, which subjects are represented by the "ST period, including rescue" since presumably all subjects who are rescued during the ST period are entered into the LT period and are therefore no longer in the ST period?

Thanks,

Rachel

From: pamela.smith@bms.com [mailto:pamela.smith@bms.com]

Sent: Tuesday, December 23, 2008 5:39 PM

To: Hartford, Rachel; Joseph Lamendola; Patrice E Todd

Subject: Re: Clinical IR for saxagliptin NDA 22-350

Rachel,

We are urgently seeking clarification (please see below) of several of the Clinical Information Requests received December 19, so that we can provide timely responses. Please copy Joe Lamendola and Patrice Todd in any correspondence as I will not have email access on December 24 and will have somewhat restricted access the following week. Thanks, and again, Happy Holidays.

Pam

3/9/2009

The Sponsor is seeking clarification regarding several of the questions received from the Agency December 19, 2008. We will appreciate a rapid response so that we can proceed with the requested analyses.

1. Please provide analyses of the occurrence of adverse events of rash (all rash terms) in your Phase 3 clinical trial program. Specifically:

- For the pool of all completed Phase 3 clinical trials (controlled portion only), provide the number and percentage of patients who experienced any event of rash (any term that included the word "rash").

Clarification request: The Longterm Extension portion of the Phase 3 clinical Trials (LT) was blinded to the investigator and to the patient while the Short Term (ST) 24 week portion was also blinded to the Sponsor. The Sponsor proposes that the analysis include events in the Short Term and the Long Term (ST + LT), including events after rescue. Does the Agency agree?

3. Resubmit the MACE table provided in the "Response to day 74 Letter dated 12-Sep-2008" using only ST data.

Clarification request: The Sponsor proposes that the MACE analysis include the ST experience (excluding rescue), similar to the experience reported in the ST CSRs (see clarification in Question 5 for further details). Does the Agency agree?

5. In addition to the data provided in Summary of Clinical Safety 2.3.7A, please provide the placebo-controlled pooled safety data, up to week 24, excluding rescue.

Clarification Request: The 24 week portions of the Phase 3 clinical trials were designed such that patients could have their final ST visit within an accepted window (+/- 3 days) around the targeted Week 24 timepoint. In analyses of AEs (ST, excluding rescue) from the ST CSR and SCS, events can be included that occur after Day 168 (Week 24) if the onset date is within 1 day (30 days for SAEs) post the latter of (a) the last ST dose, (b) the last ST visit, but before the LT treatment period. The Sponsor proposes to include all ST data up to, but excluding, rescue (similar to the experience reported in the ST CSRs, see clarification proposed to Question 3--the ST MACE analysis). Does the Agency agree?

6. In addition to the data provided in Summary of Clinical Safety 2.3.7B, please provide the table with AEs, excluding rescue.

Clarification Request: The table in the Summary of Clinical Safety 2.3.7B excludes rescue. Does the Agency agree that this analysis will be sufficient?

Hartford, Rachel wrote:

Pam,

Below are a few more Clinical questions for saxagliptin NDA 22-350. We look forward to your responses.

Hope you have a Happy Holiday,

Rachel

1. Please provide analyses of the occurrence of adverse events of rash (all rash terms) in your Phase 3 clinical trial program. Specifically:

- For the pool of all completed Phase 3 clinical trials (controlled portion only), provide the number and percentage of patients who experienced any event of rash (any term that included the word "rash").

- Comparisons should include all saxagliptin vs all control, saxagliptin vs placebo, and saxagliptin vs active control

- Provide a listing of all included terms

- Provide separate analyses for serious adverse events, and for serious + nonserious events

- Provide information on the incidence of combined rash events by saxagliptin dose

- Separate from the pooled analysis, provide the incidence of any rash event by treatment arm for the controlled portion of each individual completed Phase 3 trial.

2. Clarify why the following subjects were not classified as having a MACE event, and resubmit the table of MACE events incorporating these subjects:

-CV181011-10-459: narrative uses the term "acute coronary syndrome"

-CV181038-87-811: narrative describes discharge diagnosis "extensive AW STEMI"

3. Resubmit the MACE table provided in the "Response to day 74 Letter dated 12-Sep-2008" using only ST data.

4. Update the MACE table previously submitted to include events from 120 day safety update. For each group, provide N and exposure data.

5. In addition to the data provided in Summary of Clinical Safety 2.3.7A, please provide the placebo-controlled pooled safety data, up to week 24, excluding rescue.

6. In addition to the data provided in Summary of Clinical Safety 2.3.7B, please provide the table with AEs, excluding rescue.

7. For Table 2.3.2.1A and 2.3.2.1B in the Summary of Clinical Safety, please provide the ST period data, including rescue.

8. Explain why "tongue ulceration" was not included in the pre-defined list of PTs? How many subjects were reported to have "tongue ulceration"?

9. Provide narratives for the following placebo subjects with Cardiovascular AEs: CV181039-222-1033, CV181040-127-1070, CV181014-150-475, and CV181039-1810-2210.

10. Provide more information regarding cardiac enzymes on the day of the CV event for the following subjects: CV181040-149-862 and CV181014-154-911 (event listed in 120 day safety update).

11. In reference to "Response to FDA Request dated 3-Dec-2008," it is mentioned that the PT "cardiac failure" was not included as part of the pre-specified MedDRA CV PT list used to generate Table 2.3.7A. Please explain why this term (and possible other similar terms) were not included. Furthermore, what types of events were intended to be captured in Table 2.3.7?

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

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/s/

Rachel E Hartford
3/17/2009 03:05:43 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 22, 2008 2:06 PM
To: 'pamela.smith@bms.com'
Subject: Possible statistical error

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Our statistician believes that there is an error in the tmdsc011.xpt dataset mentioned below.

There is one subject (CV181011-101-531) on the disposition dataset that is not in other datasets in the submission. Also there is a subject (CV181011-37-531) missing from the disposition dataset who is on other datasets in the submission. From the data values, we believe these two subjects are actually one subject and that the patient number on the disposition file is incorrect (should be "37" instead of "101"). This is an unusual mistake so we would like you to 1) confirm the error and 2) check the other disposition datasets for similar errors.

The statistician requests confirmation of the error today. I will also try to reach you by phone.

Thank you,

Rachel

From: pamela.smith@bms.com [<mailto:pamela.smith@bms.com>]
Sent: Friday, December 12, 2008 1:58 PM
To: Hartford, Rachel
Subject: Re: Dataset Location Request

Dear Rachel,

We have checked our documentation, and we have located the datasets as follows for CV181011:

The dataset tmdsc011.xpt can be found in 5.3.5.1, STF CV181011, analysis dataset.

Please let me know if you still have a problem locating them. Thanks,

Pam

Hartford, Rachel wrote:

Pam,

Your November 3, 2008, submission contained responses to questions 2, 5, 11, 12, 16c, and 16f in our September 12, 2008, information request letter. It was indicated that disposition datasets called tmdsc0xx were submitted for each study. We are unable to locate the dataset for Study CV181001 in the 5.0 folders. Please provide additional information on the location of these datasets. If the datasets are not in the application, please contact me prior to submitting them.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

Rachel E Hartford
3/17/2009 03:08:01 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, December 19, 2008 1:48 PM
To: 'pamela.smith@bms.com'
Subject: Clinical IR for saxagliptin NDA 22-350

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Below are a few more Clinical questions for saxagliptin NDA 22-350. We look forward to your responses.

Hope you have a Happy Holiday,

Rachel

1. Please provide analyses of the occurrence of adverse events of rash (all rash terms) in your Phase 3 clinical trial program. Specifically:

- For the pool of all completed Phase 3 clinical trials (controlled portion only), provide the number and percentage of patients who experienced any event of rash (any term that included the word "rash").
- Comparisons should include all saxagliptin vs all control, saxagliptin vs placebo, and saxagliptin vs active control
- Provide a listing of all included terms
- Provide separate analyses for serious adverse events, and for serious + nonserious events
- Provide information on the incidence of combined rash events by saxagliptin dose
- Separate from the pooled analysis, provide the incidence of any rash event by treatment arm for the controlled portion of each individual completed Phase 3 trial.

2. Clarify why the following subjects were not classified as having a MACE event, and resubmit the table of MACE events incorporating these subjects:

- CV181011-10-459: narrative uses the term "acute coronary syndrome"
- CV181038-87-811: narrative describes discharge diagnosis "extensive AW STEMI"

3. Resubmit the MACE table provided in the "Response to day 74 Letter dated 12-Sep-2008" using only ST data.

4. Update the MACE table previously submitted to include events from 120 day safety update. For each group, provide N and exposure data.

5. In addition to the data provided in Summary of Clinical Safety 2.3.7A, please provide the placebo-controlled pooled safety data, up to week 24, excluding rescue.

6. In addition to the data provided in Summary of Clinical Safety 2.3.7B, please provide the table with AEs, excluding rescue.

7. For Table 2.3.2.1A and 2.3.2.1B in the Summary of Clinical Safety, please provide the ST period data, including rescue.

8. Explain why "tongue ulceration" was not included in the pre-defined list of PTs? How many subjects were reported to have "tongue ulceration"?

9. Provide narratives for the following placebo subjects with Cardiovascular AEs: CV181039-222-1033, CV181040-127-1070, CV181014-150-475, and CV181039-1810-2210.

10. Provide more information regarding cardiac enzymes on the day of the CV event for the following subjects: CV181040-149-862 and CV181014-154-911 (event listed in 120 day safety update).

11. In reference to "Response to FDA Request dated 3-Dec-2008," it is mentioned that the PT "cardiac failure" was not included as part of the pre-specified MedDRA CV PT list used to generate Table 2.3.7A. Please explain why this term (and possible other similar terms) were not included. Furthermore, what types of events were intended to be captured in Table 2.3.7?

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

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/s/

Rachel E Hartford
3/17/2009 02:42:16 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, December 11, 2008 1:56 PM
To: 'pamela.smith@bms.com'
Subject: CMC information requests for saxagliptin NDA 22-350

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Glad to hear you had a Happy Thanksgiving. I enjoyed the Holiday with my family in Alabama. We have several more CMC information requests for saxagliptin NDA 22-350.

Drug Substance

1. Add analytical procedures and acceptance criteria for () in the saxagliptin drug substance regulatory specification to comply with §21 CFR 314.50(d)(1)(i). **b(4)**
2. Report measured amounts of the potential () in the final certificates of analysis of the drug substance and add this control to the drug substance regulatory specification.
3. Provide information on the qualified vendors, source species, and characterization of () and any other () used in the manufacture of saxagliptin. **b(4)**
4. Provide copies of complete certificates of analysis (including batch information and analytical data) for the lots () of the starting materials used in the manufacture of the drug substance. Indicate the proposed expiry period or re-test period for these starting materials.

b(4)

Drug Product

5. Add analytical procedures and acceptance criteria for Dissolution, Ratios of the () in the drug product regulatory specification to comply with §21 CFR 314.50(d)(1)(ii)(a). **b(4)**
6. Clarify whether the ratios of the () **b(4)**
7. Indicate the location in the application or provide comparative validation data indicating the equivalence of Identification by HPLC versus Identification by UV.
8. Provide an example of the UV-Vis profile for the standard saxagliptin solution between () indicating the wavelength of the maximum absorbance and the calculated extinction coefficient for saxagliptin. **b(4)**
9. Separate the X-ray diffraction patterns and label the peaks in figures 3.2.P.2.2.4.F01 and F02 and figures 3.2.P.2.2.4.F04 and F05.
10. Provide working drawings for the proposed blister and lidding packaging.
11. Provide graphical trend analyses for the Moisture Content and Dissolution data for all strengths in all container/closures.

Labeling

12. Revise the respective proposed container labeling (side panel) for each tablet strength to read:

(
or

)

b(4)

b(4)

13. An expiry period for the 2.5 mg saxagliptin dosage strength tablet packaged in blisters will not be granted until such time as you intend to market this presentation.

Comparability Protocol

14. The lack of a specific rationale, details, methods, and discussion of post-change actions to re-validate the design space and model(s) does not allow for a complete and meaningful evaluation of the proposed comparability protocols; we strongly recommend that you withdraw the [redacted] from the application at this time and submit them at a later, post-approval date with complete supporting information.

b(4)

Additional Comments on the Drug Product QbD

15. In reference to the two DOE's presented in table 3.2.P.2.3.3.T20, provide data to show what are the significant parameters and if there is any interaction between the parameters. Indicate if the DOE data was used to develop any predictive regression model. If so, provide statistical analysis of the DOE data e.g. R2, regression coefficient etc.
16. It is noted that the PAR for coating parameters at commercial scale [redacted] was verified using an active to coating material ratio of 1:4 (refer table 3.2.P.2.3.3.T21). If available, provide data to show that these ranges would be acceptable when using an active to coating material ratio of 1:8.
17. Provide details about the experimental design presented in table 3.2.P.2.3.3.T21, e.g. type of design, number of replicates, number of factors evaluated, observance of any interactions. In addition, if available provide a statistical analysis of the data from this DOE.

b(4)

Thank You,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

Rachel E Hartford
3/17/2009 02:51:40 PM
CSO

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, December 03, 2008 11:24 AM
To: 'pamela.smith@bms.com'
Subject: Information Request for saxagliptin NDA 22-350

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Hope you had a Happy Thanksgiving. We have an additional request for saxagliptin NDA 22-350. Explain the discrepancy between the number of events as listed in Table 2.3.7A of the Summary of Clinical Safety and Table 1 in the "Response to FDA day 74 Letter" (page 8). As one example, in Table 2.3.7.A, for Study CV181014, there are 0 AEs listed under saxa 10mg, whereas there are 4 MACE events listed in Table 1. Please review and detail each difference between these tables.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, December 01, 2008 11:49 AM
To: 'pamela.smith@bms.com'
Cc: 'joseph.lamendola@bms.com'
Subject: CMC Information Requests

Follow Up Flag: Follow up
Flag Status: Purple

Attachments: 22350 saxagliptin CMC IR Request.doc

Pam,

The attached WORD document contains several CMC information requests. Please call if you have any questions.

Hope you had a wonderful Thanksgiving.

Thank you,

Rachel



22350 saxagliptin
CMC IR Reque...

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, November 21, 2008 11:20 AM
To: 'pamela.smith@bms.com'
Subject: Clinical Pharmacology Request for Saxagliptin

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

We have an additional request from Clinical Pharmacology for Saxagliptin NDA 22-350. Please submit the Nonmem "myinf.n.f" file used for the population PK analysis: \$SUBROUTINES ADVAN4 TRANS4 INFN=/global/pkms/bin/myinf.n.f

Hope you enjoy your time off.

Thank you,

Rachel

Rachel E. Hartford

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

Food and Drug Administration

rachel.hartford@fda.hhs.gov

301-796-0331 (phone)

301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, October 03, 2008 10:53 AM
To: 'pamela.smith@bms.com'
Subject: Requested Clarification

Follow Up Flag: Follow up
Flag Status: Purple

Pam,

In response to your requested clarification of question three in the filing letter, please provide the SAE narratives for the placebo and comparator groups. I am still awaiting the response to your statistical question.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, October 08, 2008 8:05 AM
To: 'pamela.smith@bms.com'
Subject: FW: Clarification request for NDA 22-350 Saxagliptin
Follow Up Flag: Follow up
Flag Status: Purple

Pam,

Provide disposition data for both segments of the trials . If there are doubts about how to set up the datasets, send in a sample before creating all the datasets.

Sincerely

Rachel

From: pamela.smith@bms.com [mailto:pamela.smith@bms.com]
Sent: Tuesday, October 07, 2008 4:51 PM
To: Hartford, Rachel
Subject: Re: Clarification request for NDA 22-350 Saxagliptin

Rachel,

I have worked with our saxagliptin Biostatistics Lead provide this text for the clarification we are seeking:

Reference is made below to Biostatistics items #11 and #12 from the saxagliptin Day 74 letter in which the Agency requested Kaplan-Meier curves by treatment group for time to discontinuation for the six pivotal studies (CV181011, -013, -014, -038, -039, and -040) and also requested datasets (xpt files) containing disposition information **for the double blind portion of the trials...."**

Each of these six trials had a 24 week double blind "Short Term" (ST) phase for the primary efficacy and safety analysis. Subjects in each treatment group continued after 24 weeks, or after rescue medication was added, into a "Long Term" (LT) extension phase. In the LT extension for each of these studies, subjects and investigators remained blinded to study drug.

BMS understands that (a) the datasets requested in item #12 support the requests for the analyses in item #11; and (b) proposes that the analyses and datasets in these items include both the ST & LT phases combined for each study. Is this approach acceptable to the Agency?

I hope this clarifies our question.

Pam Smith



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-350

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

Dear Dr. Smith:

Please refer to your new drug application (NDA) dated June 30, 2008, received June 30, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for saxagliptin tablet, 2.5 mg and 5 mg.

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 **April 30, 2009**.

During our filing review of your application, we identified the following potential review issues and have the following requests for additional information:

Clinical

1. Submit a revised Table 1.2.3A (page 51 of the summary of clinical safety) that outlines exposure to study drug overall and by doses according to the following groups: ≥ 24 weeks, ≥ 52 weeks.
2. Provide narratives for all Dermatologic adverse events (AEs), including more specific information about the appearance and location (generalized vs. localized) of each AE.
3. As discussed in the preNDA meeting, provide narratives for all serious adverse events, not just those you consider treatment-related. As an example, in the Study Report for CV181011 (page 174), it appears that you have only provided subject narratives describing Serious Adverse Events (SAEs) that were reported as related to study drug and SAEs of special interest.

4. Explain the criteria used in coding preferred terms used for your cardiovascular adverse events analyses (page 181 of the summary of clinical safety).
5. Provide narratives for all subjects with potential cardiac preferred terms that may have been classified under other System-Organ Classes (SOCs), such as “chest pain” and preferred terms related to abnormal electrocardiograms.
6. List cardiovascular events by type (e.g., “ischemia-related”, “heart rate/rhythm-related”, “heart failure-related”, and “other”) for your controlled Phase 2/3 database using standardized MedDRA queries (SMQs) for ischemic heart disease. Include a detailed description of the methodology used (e.g., which preferred terms were included).
7. For a composite variable MACE (cardiovascular-death, non-fatal myocardial infarction, and non-fatal stroke) using the controlled Phase 2/3 database, show the number of people with at least one MACE event and provide both the total number of randomized patients and the patient-year exposure for the various treatment groups. Please show these numbers both by individual study and pooled.
8. Submit a summary table of all planned and ongoing studies (including expected completion dates) if this is not included in the NDA already. If the information is in the NDA, please indicate where it is located.
9. Submit a table of exposures broken down by clinical development Phase (1, 2, and 3) with the following variables: total subjects exposed to any dose of saxagliptin, dosage range of saxagliptin, range of days on saxagliptin, and mean number of days on saxagliptin.

Clinical Pharmacology

10. Saxagliptin is a chiral molecule with four chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. We recommend you address the chiral conversion using a stereo-specific assay for detection of saxagliptin and its isomer.

Biostatistics

11. Provide Kaplan-Meier curves by treatment group for time to discontinuation for Studies CV181011, CV181013, CV181014, CV181038, CV181039, and CV181040.
12. Provide disposition datasets (xpt files) for Studies CV181011, CV181013, CV181014, CV181038, CV181039, and CV181040 which contain a single record per patient and provide disposition information for the double blind portion of each of these trials. Only patients who were randomized and entered the double-blind segment should be included in the dataset. This dataset should include both a coded numeric variable (like NNCPRNN on the raw dataset STAT) and a character variable showing the reason for

discontinuation. A variable for time on study and a variable for completer status should also be included (these variables should allow FDA to reproduce the Kaplan-Meier curves requested above). Variables for region, country and site should be included along with the usual demographic variables.

Chemistry, Manufacturing, and Controls

13. Confirm that the manufacturing and testing facilities listed in Form FDA 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product.
14. Clarify whether the 2.5 mg tablets will be packaged in blisters because this packaging is not in the proposed labeling even though this packaging is listed for this dosage strength in the Container Closure System and Stability sections of the NDA.
15. Provide references to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product.
16. Provide the following or their location in the NDA:
 - a) Physical dimensions of the finished tablets.
 - b) Stability information on the potential b(4)
 - c) Characterization information on saxagliptin hydrochloride, which is the active ingredient form in the final drug product. The information should include structural and physicochemical characterization, details on manufacturing conditions that lead b(4)
 - d) Stability information on the chirality of the molecule during the drug product manufacture and storage to support the omission of chirality testing in the drug product specification.
 - e) The characterization report, including data and analysis, on the comparability between metformin and saxagliptin. The information should include, at minimum, structural and physicochemical characterization of the active ingredients, their comparative stability pathways and products. b(4)
 - f) Data to support your statement that the saxagliptin hydrochloride b(4)

b(4)

17. Regarding the pharmaceutical development information:

- a) All data, figures, graphs, and tables provided in section 3.2.P.2 must be identified in their captions as being generated using saxagliptin or metformin.
- b) Was the predictive coating model developed using a design space generated for metformin or saxagliptin?
- c) How much of the process model, used to extend the design space, is based on metformin data?
- d) Indicate which aspects/parameters of the control strategy are based on data generated using metformin.

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, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional 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.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients from 10 years of age up to 18 years of age. Please submit a request that addresses the 0 to 9 years age group.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

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/

Mary Parks
9/12/2008 11:49:14 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-350

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

7/21/08

Dear Dr. Smith:

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: ONGLYZA (saxagliptin) Tablet 2.5 mg, 5mg

Date of Application: June 30, 2008

Date of Receipt: June 30, 2008

Our Reference Number: NDA 22-350

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 August 29, 2008, 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/oc/datacouncil/spl.html>. 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

NDA 22-350

Page 2

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
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/

Rachel E Hartford
7/21/2008 09:22:25 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 63,634

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) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for saxagliptin capsules (BMS-477118).

We also refer to the meeting held on November 14, 2007, between representatives of your firm and this agency. 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) 796-1280.

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 - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 14, 2007
TIME: 3:00 P.M. – 4:00 P.M.
LOCATION: White Oak Campus, Silver Spring, MD
APPLICATION: IND 63,634
DRUG NAME: Saxagliptin (BMS-477118) Capsules
TYPE OF MEETING: Pre-NDA; Type B

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Julie Marchick, MPH

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolism and Endocrinology Products:

Mary Parks, MD	Director
Hylton Joffe, MD, MMSc	Acting Diabetes Clinical Team Leader
Robert Misbin, MD	Medical Officer
Brenda Gierhart, MD	Medical Officer
Todd Bourcier, PhD	Pharmacology/Toxicology Team Leader
Fred Alavi, PhD	Pharmacology/Toxicology Reviewer
Julie Marchick, MPH	Regulatory Project Manager

Office of Biostatistics:

J. Todd Sahlroot, PhD	Biostatistics Team Leader
Lee Ping Pian, PhD	Biostatistics Reviewer

Office of Clinical Pharmacology:

Jaya Vaidyanathan, PhD	Clinical Pharmacology Reviewer
Sally Choe, PhD	Clinical Pharmacology Team Leader

Office of Surveillance and Epidemiology:

Cheryl Campbell	Project Manager
-----------------	-----------------

EXTERNAL CONSTITUENT ATTENDEES:

Robert Wolf, MD	Vice President, Global Clinical Development – CV and Metabolics, BMS
Roland Chen, MD	Group Director, Global Clinical Research – CV and Metabolics, BMS
Fred Fiedorek, MD	Vice President, Global Clinical Research – CV and Metabolics, BMS
David Boulton, PhD	Associate Director, Clinical Discovery, BMS

Liping Zhang, PhD	Associate Director, Statistic Modeling and Simulation, BMS
Mary Beth Blauwet, DrPh	Associate Director, Global Biometrics Sciences, BMS
David Henry, PhD	Executive Director, Global Biometrics Sciences, BMS
Joseph Lamendola, PhD	Vice President, Global Regulatory Sciences, BMS
Pamela Smith, MD	Group Director, Global Regulatory Sciences, BMS
Margo Herron	Director, Regulatory Affairs, Regulatory Relations and Policy, BMS
Howe Li, MD	Medical Director, Global Pharmacovigilance & Epidemiology, BMS
Brian Daniels, MD	Senior Vice President, Global Clinical Development, BMS
Cary McConlogue, PhD	Associate Director, Project Planning and Management, BMS
Tomas Odergren, MD, PhD	Global Product Vice President, Development Projects, AstraZeneca
Margaret Melville, MS	Senior Global Regulatory Lead, AstraZeneca
Peter Ohman, MD	Senior Medical Science Director, AstraZeneca
Artist L. Parker, MD, MPH	Medical Director, Safety Surveillance, Clinical Drug Safety, AstraZeneca

BACKGROUND:

IND 63,634 for saxagliptin was submitted by Bristol-Myers Squibb Company on November 8, 2001. Saxagliptin is a dipeptidyl peptidase IV (DPP-IV) inhibitor being developed for the treatment of hyperglycemia in patients with type 2 diabetes mellitus. An End-of Phase 2 Meeting was held on July 27, 2005.

Proposed Indications:

Monotherapy

As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Add-on Combination Therapy

In patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, a thiazolidinedione, or a sulfonylurea, when the single agent, plus diet and exercise, does not provide adequate glycemic control.

Initial Combination Therapy

As initial therapy in combination with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus whose hyperglycemia is inadequately controlled on diet and exercise alone.

Phase 3 Studies:

Monotherapy

Study CV191041 (Treatment-Naïve Diabetic Subjects): *Mechanism of Action and Efficacy of Saxagliptin (BMS-477118) in the Treatment of Type 2 Diabetic Patients.*

Study CV181011 (Treatment-Naïve Diabetic Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise.*

Study CV18038 (Treatment-Naïve Diabetic Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise.*

Combination Therapy

Study CV181014 (Metformin Failure Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.*

Study CV181013 (Saxagliptin Combination with Thiazolidinedione): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone.*

Study CV181040 (Saxagliptin Add-On Prior to Titration of Sulfonylurea): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Glyburide in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Glyburide Alone.*

Study CV181039 (Initial Combination Therapy for Treatment-Naïve Subjects with Type 2 Diabetes Mellitus): *A Multicenter, Randomized, Double-Blind, Active Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin XR as Initial Therapy versus Saxagliptin Monotherapy and Metformin XR Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Diet and Exercise.*

MEETING OBJECTIVES:

To discuss the format and content of the saxagliptin NDA.

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 November 9, 2007, follow in bold font. The Sponsor's responses, provided to the Division on November 14, 2007, prior to the meeting, follow in bold italic font. A summary of the meeting discussion is underlined.

QUESTION 1

Does the Agency agree that the proposed approach to the content, data pooling strategy, and analysis strategy for the Summary of Clinical Efficacy will be acceptable for filing the NDA?

Division Response: The primary variable is HbA1c. There are several secondary variables based on efficacy. Some of these may be considered exploratory and not appropriate in labeling.

The proposed approach for data pooling is acceptable for filing but will not be the Agency's primary review focus for evaluating efficacy. Statistical inferences will be drawn primarily from individual studies, not pooled data.

QUESTION 2

Does the Agency agree that the proposed approach to the content, data pooling strategy, and analysis strategy for the Summary of Clinical Safety will be acceptable for filing the NDA?

Division Response: Pooling of safety data from similar studies (e.g., the two 24-week monotherapy studies) is appropriate. However, pooling data from trials that are not similar (e.g., monotherapy trials pooled with add-on therapy trials or pooling of different add-on therapy trials) is of limited value because mixing of data from disparate treatments will limit the ability to detect saxagliptin-related safety signals.

Sponsor Response: The Sponsor appreciates the comment about the potential limitations to the value of pooling data from dissimilar trials (e.g. monotherapy pooled with add on therapy). Based on the Agency's comments, the Sponsor may choose to delete some of the planned analyses for that pooled population.

The Sponsor does however see some potential value in this pool.

- ***Permits assessment of safety in clinically-relevant subgroups***
- ***Permits assessment of more uncommon events***
- ***Facilitates assessment of long-term safety***

Meeting Discussion: The Division stated that some pooled datasets may be more informative than others and that the Division will not necessarily review pooled datasets that have significant limitations. The Division acknowledged the value of pooling certain

studies, such as the monotherapy studies. The Division stated that the Sponsor may submit an updated pooling plan for review by the Division.

QUESTION 3

Does the Agency agree with the proposed approach to the analysis of events of special interest?

Division Response: Changes in lymphocytes, platelets, infections and skin effects are listed as events of special interest. For infections, please also summarize the data by organism type (bacterial, viral, fungal).

Sponsor Response: Overall approach will include two different methods to analyze infections by organism type.

Approach 1:

- *Examine AEs [adverse events] that fall within SOC [system organ class] “Infections and Infestations”*
- *Categorize for type of causative organism based on PT [preferred term] (e.g., candidiasis → fungal infection)*
- *Primary limitation – PTs are frequently non-specific, and do not allow categorization by causative type of organism (e.g., “pneumonia”)*

Approach 2:

- *Special CRFs [case report forms] are used to collect information on infection-related AEs based on pre-specified list of MedDRA PTs and where:*
 - *investigator assigned AE intensity as “severe” or “very severe”, or*
 - *the case was determined to be of clinical interest by the medical team (e.g., opportunistic infection)*
- *Special case report form includes questions that enable investigator to designate (if known) the type of causative organism (e.g., bacterial, viral, fungal)*
- **Limitations:**
 - *Forms sent out for only select infection-related AEs throughout the program*
 - *Even where forms have been completed, investigator is frequently unable to determine the type of causative organism*

Meeting Discussion: The Division stated that this approach is acceptable.

Division Response (Continued): In addition, include hypersensitivity reactions (including angioedema, angioedema-like events, and anaphylaxis) ...

Sponsor Response:

Adverse events will be summarized that correspond to medical concepts of:

- *Anaphylaxis*
- *Angioedema*
- *Angioedema-like events*

A list of preferred terms will be selected to identify each of the above events.

Meeting Discussion: The Division stated that this approach is acceptable. The list of preferred terms used for this analysis should be included in the NDA.

Division Response (continued): ...and change in liver tests as events of special interest. For suggested analyses of liver tests, please refer to the Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation (Draft Guidance), at <http://www.fda.gov/cder/guidance/7507dft.pdf>. Additional analyses may be needed after the initial review.

Sponsor Response: The following analyses will be performed for each individual study report and will be summarized in the SCS:

- *Changes from baseline summarized over all scheduled times of assessment, presenting number of subjects, means, medians, and SDs [standard deviations] for:*
 - *Alanine aminotransferase (ALT)*
 - *Aspartate aminotransferase (AST)*
 - *Alkaline phosphatase*
 - *Total bilirubin*
- *Summary of marked abnormalities by treatment group for:*
 - *ALT > 3x, 5x ULN*
 - *AST > 3x, 5x ULN*
 - *Alkaline phosphatase > 3x pre-rx and > ULN*
 - *Total Bilirubin > 2mg/dl*
- *Shift tables based on ALT and AST categories $\leq 3x$ ULN, >3 to $\leq 5x$ ULN and $> 5x$ ULN using the highest short-term treatment period value.*
- *Summary of number of subjects with ALT value $> 3x$ ULN and total bilirubin value $> 1.5x$ ULN at the same short-term treatment period assessment.*

The following analyses will be uniquely presented in the Summary of Clinical Safety for pooled analyses and Study CV181039:

- *Summary of marked abnormalities by treatment group will incorporate the additional following criteria:*
 - *ALT > 10x and 20x ULN*
 - *AST > 10x and 20x ULN*
 - *Alkaline phosphatase >1.5x ULN*
 - *Total Bilirubin > 1.5x ULN and 2x ULN (note exclusion criteria for total bilirubin ≥ 2 mg/dL)*
- *Identification of Hy's Law cases will additionally be assessed based on definition of any elevated AT of $>3x$ ULN and ALP $<2x$ ULN, and associated with an increase in bilirubin $\geq 2x$ ULN*
- *Frequency rates based on patient-years of exposure to be provided for elevation of ALT $> 3x$ ULN and Hy's Law cases*

- *Time-to-event analyses to be provided if 5 or more overall cases are observed across treatment groups within an analysis for the following categories*
 - *elevation of ALT > 3x ULN,*
 - *Hy's Law cases,*
 - *liver-related deaths and discontinuations*
- *Liver-related AEs from Phase 1/2 studies and uncontrolled open-label Phase 3 experience will be presented in SCS separately from pooled analyses*

Meeting Discussion: The Division requested that the Sponsor use two methods to define Hy's Law – one definition should require alkaline phosphatase <2x ULN; the second definition should not have an alkaline phosphatase requirement. The Division also requested that the Sponsor provide, in easily accessible format, the actual liver test values for patients with ALT or AST >3x ULN and the actual serum creatinine values for patients with outlier values for serum creatinine. In addition, the Division requested that all laboratory values be presented in conventional (American) units.

QUESTION 4

Does the Agency agree with the proposed approach to inclusion of long-term extension data from the pivotal studies in the NDA?

Division Response: Please clarify this question. For claims regarding persistence of efficacy, we note that one interim efficacy analysis will be conducted on the long-term extension data. The purpose of this data analysis in the NDA needs clarification. The proposed responder efficacy analysis in a subset of randomized patients with HbA1c<7% at Week 24 involves a non-randomized comparison and therefore is not acceptable to support claims of persistence of effect.

Sponsor Response: The intent of this question was to gain agreement with the Agency on time points for cutting data from the long-term extensions as close to the filing date as practical.

[The Sponsor provided a proposal for long-term extension data cut-off dates for interim analyses for the pivotal phase 3 studies, shown on Slide 15 of the attached handout.]

Analyses to be summarized by individual study as follows:

- *Primary Analyses*
 - *Based on randomized subjects dataset and data from short- and long-term periods*
 - *Includes change from baseline in A1C, FPG, PP glucose AUC, 120-min PP glucose, and proportion with A1C<7% over time*
- *Secondary Analyses*
 - *Completer Analysis*
 - *Responder Analysis*
 - *The Sponsor recognizes the limitations of these secondary analyses*

Meeting Discussion: The Division is primarily concerned with limitations of the responder analysis. This analysis should not be used to make inferences about the effect of the drug. Also see Discussion following Question 7.

QUESTION 5

Does the Agency agree with the proposed plans for including subject narratives in the NDA?

Division Response: Narratives will be included for deaths, serious adverse events and discontinuations due to adverse events. Narratives for patients with lymphocyte count $\leq 750/\text{mm}^3$, platelet count $\leq 50,000/\text{mm}^3$ and fingerstick glucose ≤ 50 mg/dL seem appropriate for now. Narratives for noteworthy skin, edema and infection related adverse events will also be included. In addition, narratives should be included for patients with ALT $> 5x$ ULN or ALT $> 3 x$ ULN with bilirubin $> 2x$ ULN.

Sponsor Response: The Sponsor would like to clarify that, per ICH E3 Guidance, narratives for SAEs will be presented for related serious adverse events. The Sponsor would like to further clarify that narratives will be provided for subjects with fingerstick glucose ≤ 50 mg/dL and accompanied with symptoms of hypoglycemia. The Sponsor agrees to provide narratives for subjects with ALT $> 5x$ ULN or ALT $> 3 x$ ULN with bilirubin $> 2x$ ULN.

Meeting Discussion: The Division requested narratives for all treatment-emergent serious adverse events (regardless of investigator assessment of causality). The Sponsor should also include narratives for patients who discontinued therapy due to adverse events, and for patients with accidental injuries.

QUESTION 6

Does the Agency agree with the proposed plans for data sets and case report forms to be included in the NDA?

Division Response: Yes. Requests for other case report forms may be made during the review. Please clarify why you will not be submitting datasets in CDISC format.

Sponsor Response: Because submission of subject profiles and data tabulation datasets conforming to CDISC SDTM standards is not currently a requirement, the Sponsor has not yet developed the capability to provide data in this format.

Meeting Discussion: The Division stated that this is acceptable. The Division requested that the variable names in the datasets be clearly labeled and defined so that the reviewers will be able to understand the headings with ease.

QUESTION 7

Does the Agency agree with the proposed plans for the content and data to be included in the 4-Month Safety Update?

Division Response: In Table 9.2 of the briefing document you provide an estimated extent of exposure at NDA filing and at the 4-month safety update. Please submit a breakdown of exposures at these two time points by duration (as you have done in Table 9.2), background anti-hyperglycemic therapy (e.g., monotherapy, add-on to metformin, add-on to sulfonylurea, etc.) and by saxagliptin dose. Please submit these data prior to the face-to-face meeting, or, if that is not possible, at the face-to-face meeting.

Sponsor Response: The Sponsor provided 4 tables showing estimated saxagliptin exposure at time of proposed NDA submission and at time of proposed 4 month safety update, shown on Slides 23-26 in the attached handout.

Meeting Discussion: The Division expressed concern that the Sponsor plans to submit a lot of data in the 4 month update, particularly for the add-on to sulfonylurea and add-on to thiazolidinedione (TZD) studies. For these two studies the one-year exposures at NDA filing are rather low and will be nearly doubled at the 4 month update. The Division requested sample sizes of at least 200 patients at 50 weeks at the time of NDA filing for the monotherapy and each of the combination therapy settings. The Sponsor inquired about possibly filing the NDA at the currently proposed timepoint but without data for combination therapy with a TZD. The Division stated that the wording of the label may contain significant limitations if data on use with a TZD are not available. In addition, it would be undesirable to not have safety data in combination with a TZD as this therapy is amongst the most frequently used treatments for glycemic control in patients with type 2 diabetes. The Sponsor stated that they will recalculate the cut-off points and re-consider their proposed submission date.

Based on the Division's concerns described above, the Sponsor submitted a revised proposal on December 7, 2007, for patient exposures at the time of NDA submission and at the time of the safety update (see attached handout). The Division reviewed these slides and sent the following comments to the Sponsor on December 13, 2007: "You may submit the NDA and 4-month safety update with exposures as shown in your revised proposal. Please note that safety at lower doses (e.g., 2.5 mg) will not support safety of higher doses (e.g., 5 mg). However, safety of lower doses (e.g., 5 mg) will be supported by safety data from that dose and from higher doses (e.g., 10 mg). If safety concerns arise with higher doses, it will be a review issue as to whether there are sufficient data at lower doses to support approval."

QUESTION 8

Does the Agency agree that the updated data set for the Single-dose PK Study in Subjects with Renal Impairment is consistent with the proposed dose adjustment approach for patients with type 2 diabetes and moderate and severe renal impairment?

Division Response: The updated data set for the single-dose PK study in renal impaired subjects appears to be consistent with the proposed dose-adjustment approach in moderate and severe renal impaired patients. However, the decision will be made pending review of the data in the NDA including the renal PK study.

OTHER COMMENT 1

In the NDA, include subgroup analyses of efficacy and safety based on baseline renal function (e.g., estimated creatinine clearance <60 mL/min vs. \geq 60 mL/min).

Sponsor Response: The Sponsor agrees to conduct subgroup analyses of efficacy and safety based on baseline renal function in the monotherapy with add-on therapy pooled population and the CV181039 initial combination population. The Sponsor proposes to perform subgroup analyses based on a cutoff of estimated creatinine clearance of 80 mL/min using Cockcroft-Gault analysis.

Meeting Discussion: The Division stated that this is acceptable.

OTHER COMMENT 2

When reporting the most common adverse events, use a cut-off value of \geq 2% instead of your proposed \geq 5% cut point.

Sponsor Response: The Sponsor agrees to provide common adverse event tables using a cut-off value \geq 2%.

Meeting Discussion: The Division stated that this is acceptable.

OTHER COMMENT 3

For accidents and trauma events (e.g., car accident, falls), include an assessment of whether hypoglycemia may have contributed to the event.

Sponsor Response: Proposal for evaluation of accidents/trauma and contribution of hypoglycemia:

- *Identify cases of accidents and trauma using preferred terms*

- *Examine associated verbatim term to identify any mention of concomitant hypoglycemia that may have precipitated event*
- *Query sites for details regarding accident/trauma event*
- *Evaluation will be performed on the monotherapy with add-on therapy pooled population and the CV181039 initial combination population*

Meeting Discussion: The Division stated that this is acceptable.

OTHER COMMENT 4

For all safety tables, provide subject-year exposure in the first row of each column.

Sponsor Response: Proposal for providing subject-year exposure in safety tables:

- *Provide table of subject-year exposures for each safety population and associated dataset by treatment group*
- *Of note, exposures would be provided:*
 - *For populations and datasets used in the SCS*
 - *For safety datasets used at the clinical study level*
 - *Without curtailment at time of first event (total exposure to drug)*
- *Exposures to be presented as standalone tables (i.e., not presented on every safety table)*

The Sponsor provided example tables in attached slides number 34 and 35.

Meeting Discussion: The Division stated that this is acceptable.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENT 1

It is noted that the effect of food on saxagliptin PK was conducted with the Phase 3 formulation which is different from the proposed to be marketed formulation. The need for a bioequivalence study will be determined based on the magnitude of the differences between the two formulations.

Sponsor Response: The Phase 3 formulation and the to-be-marketed formulation are equivalent by SUPAC Guidelines [Guidance for Industry: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation] - formulations differ only by color and embossing for all tablet strengths. In vitro dissolution profiles of Phase 3 formulation and to-be-marketed formulation are equivalent. A supporting document is being provided with these slides [attached].

Meeting Discussion: The Division stated that this is acceptable.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENT 2

For clinical protocol D1680C00007, we recommend that the population PK analysis include an adequate number of patients to characterize the PK of saxagliptin and its metabolite in moderate, severe, and end-stage renal impaired patients.

Sponsor Response: The sampling plan in the -007 study will be adequate to characterize the estimated systemic exposure for saxagliptin and BMS-510849 in each individual.

- *Population PK samples (4 time points) will be collected from every subject in Study D1680C00007 (84 subjects randomized to saxagliptin)
- Population PK samples will be collected at the discontinuation visit for relevant subjects*
- *The present population PK model will be refined based on data from the single-dose clinical pharmacology renal impairment study*

A supporting document is being provided with these slides [attached].

Meeting Discussion: The Division asked the Sponsor for the justification behind the 4 population PK sampling time points in D1680C0007 study. The Sponsor explained how the modeling and simulation work supported those 4 particular sampling time points and the Division stated that that is acceptable.

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY COMMENTS

If you believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

- Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>
- Development and Use of Risk Minimization Action Plans: <http://www.fda.gov/cder/guidance/6358fnl.htm>
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: <http://www.fda.gov/cder/guidance/6359OCC.htm>

If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal (e.g., healthcare provider education materials, patient education materials, website, surveys, forms, dear healthcare professional letters, etc.).

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.
- You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

ADDITIONAL MEETING DISCUSSION

The Sponsor stated that they will provide a rationale of why a completed renal study is not critical to the NDA filing in response to the Division's letter dated July 2007. The Division directed the Sponsor to the Januvia (sitagliptin) label, which describes minor increases in serum creatinine among Januvia-treated patients with moderate renal impairment.

The Sponsor also stated that the population PK analysis from the renal study will not be included in the initial filing of the NDA.

ATTACHMENTS/HANDOUTS:

- 1) Slides¹
- 2) Response to Additional Clinical Pharmacology Comment 1¹
- 3) Response to Additional Clinical Pharmacology Comment 2¹
- 4) Sponsor's Revised Proposal for Patient Exposures²

¹Handouts provided by the Sponsor on November 14, 2007, prior to the meeting

²Provided by the Sponsor on December 7, 2007

Additional Clinical Pharmacology comment:

It is noted that the effect of food on saxagliptin PK [CV181034] was conducted with the Phase 3 formulation which is different from the proposed to be marketed formulation. The need for a bioequivalence study will be determined based on the magnitude of the differences between the two formulations.

Response

This response outlines the nature of the saxagliptin clinical and proposed commercial formulations and the differences between them. The minor differences between the saxagliptin clinical formulations and the proposed commercial formulations are not expected to have a significant impact on the product performance characteristics as determined by *in vitro* dissolution testing.

The compositions of the 10 mg saxagliptin clinical formulation employed in the Phase 3 program and the definitive food effect study (CV181034)

The composition of the 10 mg saxagliptin clinical tablets

Table 1. The 2.5 mg, and 5 mg commercial tablets also only differ from the corresponding strength clinical tablets in tablet color and the printing for identification.

Description and Composition of the Tablet Formulations Employed in the Food Effect Study and in the Phase 3 Clinical Studies

The Phase 3 drug product for saxagliptin is a film coated immediate release tablet in four strengths: 2.5 mg, 5 mg and 10 mg (as the free base). Saxagliptin film coated tablets are manufactured by () saxagliptin) onto a placebo tablet in the following sequence:

The pH of each of the coating suspensions listed above is adjusted to about ()

To facilitate blinding, all tablet strengths and the placebo tablet for the Phase 3 clinical studies appear yellow and utilize ()

b(4)

b(4)

b(4)

b(4)

Description and Composition of the Proposed Commercial Formulations

As with the clinical Phase 3 tablets, the proposed commercial tablets for saxagliptin are film coated immediate release tablets.

The differences between the Phase 3 clinical formulation used in CV181034 and the proposed commercial formulation are as follows:

1. All Phase 3 tablets are butterscotch colored for [redacted] and the color for the proposed commercial [redacted]
2. The proposed commercial tablet will be printed with [redacted] on one side and the product code on the other using a blue printing ink that contains [redacted]

b(4)

b(4)

The 2.5 mg, and 5 mg commercial tablets also only differ from the corresponding strength clinical tablets in the color of the third layer and the printing for identification.

Dissolution Profiles

The dissolution profiles of all Phase 3 formulations are rapid (>85% dissolved in 30 minutes) and thus dissolution of saxagliptin is not the rate limiting factor for its bioavailability. Saxagliptin is a highly soluble compound relative to the clinical dose (>20 mg/mL from pH 1 to 9). In spite of poor Caco-2 permeability (18 nm/sec), saxagliptin shows good oral bioavailability. Approximately 75% of a radiolabeled oral dose of saxagliptin was recovered in the urine and most of the radioactivity in the feces was from oxidative metabolites, presumably excreted in the bile (CV181004) suggesting extensive absorption of saxagliptin from the gastrointestinal tract. Thus, while saxagliptin is technically classified as a BCS Class 3 compound, its high extent of oral absorption suggests it can be considered a borderline BCS Class I compound. Thus, *in vitro* dissolution testing is an appropriate method for examining the impact of small differences in saxagliptin formulations.

In order to bridge the Phase 3 formulations with the proposed commercial formulations, *in vitro* dissolution profiles for Phase 3 formulations and proposed commercial formulation for all proposed strengths was generated in at least three dissolution media (pH 1.0, 4.5 and 6.8) to demonstrate dissolution rate similarity. The dissolution data are shown for the 2.5 mg, 5 mg and 10 mg [redacted] and clinical formulations in Tables 2.1A through 2.3B. The dissolution method used to generate the data in the different media was a USP Apparatus 2, with paddles at 50 rpm.

b(4)

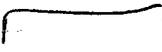
On comparing the dissolution results of the clinical tablets and the proposed commercial tablets in different dissolution media, it is confirmed that the minor differences of color in

the ϵ and imprinting do not have any impact on the dissolution profile of saxagliptin tablets and would therefore not be expected to have a detectable impact on *in vivo* bioavailability.

b(4)

Table 1: Compositions of the 10 mg Saxagliptin Clinical (Phase 3) Saxagliptin Film Coated Tablet Used in the Food Effect Study (CV181034)

b(4)

Component	Compendial Reference	Function	Quantity per unit dose (mg)	
			10 mg Clinical Tablet PIN: 477118-K010-122	
Lactose Monohydrate	NF			
Microcrystalline Cellulose	NF			
Croscarmellose Sodium	NF			
Magnesium Stearate	NF			
	NC			
	NC			
Saxagliptin ^c	NC			
	USP			
	FDC			
Tablet Weight			ca. 234.7	

b(4)

NC = non compendial; q.s. = quantity sufficient; ca = calculated average



b(4)

Table 2.1A: Dissolution of Saxagliptin Film Coated Tablets, 2.5 mg Proposed Commercial Lot No. 6C4326X in pH 1.2, 4.5 and 6.8

Time, Minutes	% Saxagliptin Dissolved (Mean \pm SD results of 12 tablets)		
	pH 1.2, 0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
5	65 \pm 6.79	69 \pm 5.39	65 \pm 4.87
10	84 \pm 7.97	88 \pm 7.15	83 \pm 6.38
15	88 \pm 7.28	92 \pm 5.59	89 \pm 5.11
20	90 \pm 6.47	94 \pm 4.80	92 \pm 4.25
30	93 \pm 5.33	96 \pm 4.27	94 \pm 3.45
60	97 \pm 4.23	99 \pm 3.71	97 \pm 3.04

Table 2.1B: Dissolution of Saxagliptin Film Coated Tablets, 2.5 mg Clinical Batch No. 6D12066 in pH 1.2, 4.5 and 6.8

Time, Minutes	% Saxagliptin Dissolved (Mean \pm SD results of 12 tablets)		
	pH 1.2, 0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
5	62 \pm 4.29	65 \pm 3.32	60 \pm 4.45
10	81 \pm 6.50	88 \pm 3.51	80 \pm 5.04
15	88 \pm 5.94	94 \pm 3.36	87 \pm 4.36
20	91 \pm 4.77	97 \pm 3.69	91 \pm 3.74
30	94 \pm 3.25	98 \pm 3.95	94 \pm 2.92
60	97 \pm 1.92	100 \pm 4.15	96 \pm 2.37

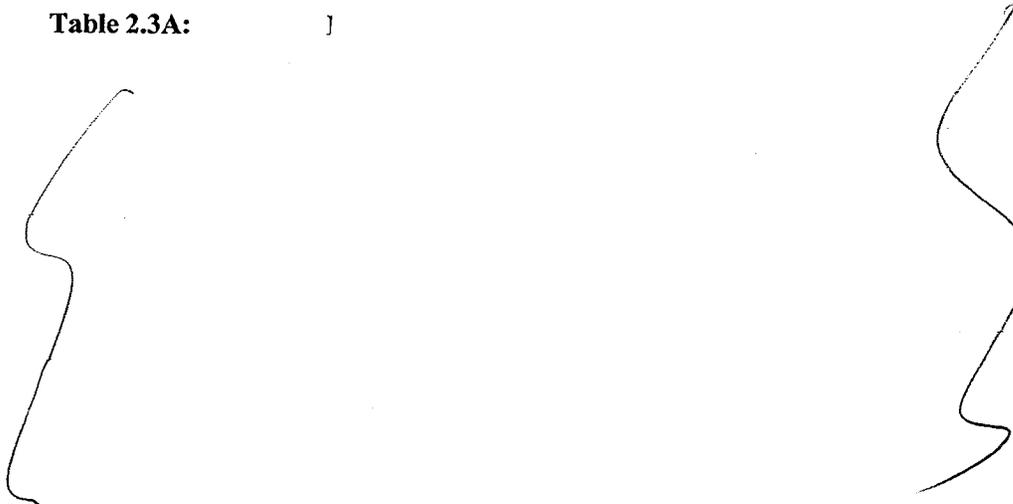
**Table 2.2A: Dissolution of Saxagliptin Film Coated Tablets, 5 mg
Proposed Commercial Lot No. 6C4330X in pH 1.2, 4.5
and 6.8**

Time, Minutes	% Saxagliptin Dissolved (Mean \pm SD results of 12 tablets)		
	pH 1.2, 0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
5	61 \pm 5.94	65 \pm 4.80	62 \pm 3.40
10	82 \pm 8.66	86 \pm 6.63	84 \pm 5.12
15	88 \pm 6.89	92 \pm 5.77	91 \pm 5.20
20	91 \pm 5.66	94 \pm 5.02	93 \pm 4.77
30	94 \pm 4.50	96 \pm 4.19	95 \pm 4.06
60	98 \pm 3.17	98 \pm 3.26	97 \pm 3.17

**Table 2.2B: Dissolution of Saxagliptin Film Coated Tablets, 5 mg
Clinical Batch No. 6D19416 in pH 1.2, 4.5 and 6.8**

Time, Minutes	% Saxagliptin Dissolved (Mean \pm SD results of 12 tablets)		
	pH 1.2, 0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
5	59 \pm 4.60	63 \pm 3.61	58 \pm 3.51
10	83 \pm 4.92	88 \pm 5.21	81 \pm 4.51
15	92 \pm 4.43	95 \pm 4.92	89 \pm 4.39
20	95 \pm 3.71	96 \pm 4.41	92 \pm 3.85
30	97 \pm 2.85	98 \pm 3.74	94 \pm 3.37
60	100 \pm 2.04	99 \pm 3.17	97 \pm 3.39

Table 2.3A:



b(4)

**Table 2.3B: Dissolution of Saxagliptin Film Coated Tablets, 10 mg
Clinical Batch No. 5L08927 in pH 1.2, 4.5 and 6.8**

Time, Minutes	% Saxagliptin Dissolved (Mean ± SD results of 12 tablets)		
	pH 1.2, 0.1N HCl	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
5	74 ± 6.86	78 ± 6.50	70 ± 8.21
10	89 ± 4.82	97 ± 5.08	92 ± 6.08
15	98 ± 4.81	101 ± 5.05	98 ± 5.75
20	99 ± 4.25	102 ± 5.05	99 ± 4.84
30	100 ± 3.02	102 ± 5.11	100 ± 4.50
60	101 ± 2.62	102 ± 5.13	100 ± 4.39

Additional Clinical Pharmacology comment:

For clinical protocol D1680C00007, we recommend that the population PK analysis include an adequate number of patients to characterize the PK of saxagliptin and its metabolite in moderate, severe, and end-stage renal impaired patients.

Response

Population pharmacokinetic (PPK) samples will be collected at the Week 12 visit from every randomized subject in Study D1680C00007 who has not discontinued by this visit which corresponds to the end of the short-term phase of the study. Therefore, a pharmacokinetic dataset from D1680C00007 will contain data all from subjects who complete the short term phase. A total of 84 patients with renal impairment will be randomized to saxagliptin treatment. Of these, a minimum of 20 patients with moderate renal impairment, a minimum of 20 patients with severe renal impairment, and a maximum of 20 patients with end-stage renal impairment receiving dialysis treatment will be randomized. Patients who discontinue before the end of the 12 Week short-term phase will undergo Week 12 visit procedures, including PPK sampling.

PPK samples will be collected pre-dose and 1, 2, and 4 hr after administration of 2.5 mg saxagliptin at Week 12 (or at the time of discontinuation). Figure 1 shows the PPK sampling times to be used in Study D1680C00007 overlaid on the mean plasma concentration-time profiles for saxagliptin and BMS-510849 in the moderate and severe renal impairment groups from Study CV181019. For parent saxagliptin, the PPK sampling scheme in Study D1680C00007 is expected to characterize any accumulation (pre-dose sample), C_{max} (1 h) and clearance (2 h and 4 h). For BMS-510849, the PPK sampling scheme in Study D1680C00007 is expected to characterize clearance and accumulation (pre-dose sample), and C_{max} (4 h).

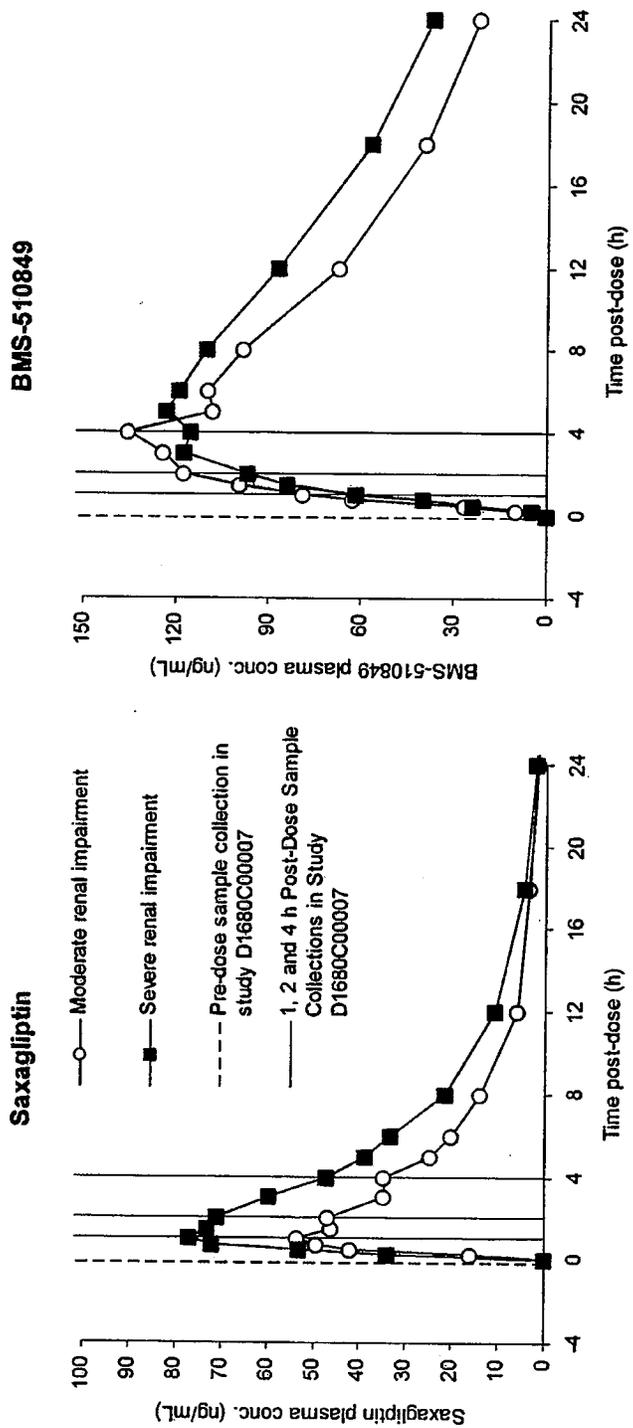
The preliminary PPK model developed to date has been built from the pharmacokinetic data of hundreds of subjects or patients with type 2 diabetes from 4 Clinical Pharmacology studies (CV1810001, CV181002, CV181018, CV181037) and 1 Phase 3 study (CV181011). These subjects or patients had normal renal function or mild renal impairment and the PPK model includes creatinine clearance as a covariate on apparent clearance. This PPK model appears to fit the data well.

Depending on the number of discontinuations without Week 12 procedures being conducted, up to 336 saxagliptin and BMS-510849 plasma concentration-time points will be available in Study D1680C00007 (120 subjects x 4 samples/subject). The single dose renal impairment study (CV181019) collected rich pharmacokinetic profiles (8 subjects in each of the normal renal function, and mild, moderate and severe renal impairment

groups, ~15 >LLQ samples/profile = 480 >LLQ samples). The data from D1680C00007 and CV181019 (up to 960 concentration time points) will be pooled to further refine the preliminary PPK model to optimally describe systemic exposures to saxagliptin and BMS-510849 at lower values of creatinine clearance. The saxagliptin and BMS-510849 systemic exposures (ie, steady-state AUC) will be estimated for each Study D1680C00007 subject completing the Week 12 visit procedures with this enhanced PPK model.

In summary, the rich pharmacokinetic data from 16 subjects with moderate or severe renal impairment (CV181019) and the sparse datasets from all patients with moderate or severe renal impairment completing the short term phase of Study D1680C00007 permits (i) characterization of the effect of renal function on apparent saxagliptin and BMS-510849 clearance and (ii) estimation of individual steady-state AUC values for saxagliptin and BMS-510849 which can be used to explore for relationships between individual exposures and efficacy/safety endpoints.

Figure 1: Pharmacokinetic Sampling Times to be used in Study D1680C00007 Overlaid on the Mean Plasma Concentration-Time Profiles for Saxagliptin and BMS 510849 in the Moderate and Severe Renal Impairment Groups from the Saxagliptin Single Dose renal Impairment Study (CV181019)



Notes: ESRD patients are expected to have similar pharmacokinetic profiles to subjects with severe renal impairment as the pharmacokinetic assessment is not done on a hemodialysis day

CV181019 data are preliminary and partial (N = 7 subjects with moderate renal impairment and 5 subjects with severe renal impairment)

Linked Applications

Sponsor Name

Drug Name

IND 63634

BRISTOL MYERS
SQUIBB

BMS-477118
SOLUTION/CAPSULE/SAXAGLIPTIN

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

/s/

JULIE C MARCHICK
12/14/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,634

Bristol-Myers Squibb Company
Attention: Gerald DiDonato, Associate Director
P.O. Box 5400
Princeton, NJ 08543-5400

Dear Mr. DiDonato:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for saxagliptin tablets.

We refer to the meeting between representatives of your firm and the FDA on April 26, 2007. This was a science-focused meeting, where you had the opportunity to present some examples of quality by design (QbD) in the development of saxagliptin, as it relates to this upcoming NDA which is part of the CMC pilot program.

The official minutes of the above 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) 796-1647.

Sincerely,

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 26, 2007
TIME: 1:30 pm – 3:00 pm
LOCATION: Food and Drug Administration, White Oak Room 1419
APPLICATION: IND 63,634
DRUG NAME: Saxagliptin tablets
TYPE OF MEETING: Type C
MEETING CHAIR: Moheb Nasr
MEETING RECORDER: Amy Bertha

FDA ATTENDEES:

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Moheb Nasr, Director
Chi-wan Chen, Deputy Directory
Blair Fraser, Director, Division of Pre-Marketing Assessment I
Christine Moore, Branch Chief, Manufacturing Sciences Branch
Su Tran, Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I
Prafull Shiromani, Chemist, Division of Pre-Marketing Assessment I
Sharmista Chatterjee, Chemist, Manufacturing Sciences Branch
Amy Bertha, Regulatory Health Project Manager

OFFICE OF COMPLIANCE

Division of Manufacturing and Product Quality
Zi Qiang Gu, Compliance Officer

EXTERNAL CONSTITUENT ATTENDEES: BMS

Robert Lipper, Vice President, Biopharmaceutics R&D
San Kiang, Director, Process R&D
Prakash Parab, Director, Manufacturing Technologies
Divyakant Desai, Associate Director, Biopharmaceutics R&D
Howard Stamato, Associate Director, Biopharmaceutics R&D
Anna Coslett, Director, Technical Operations Quality Control/Quality Assurance
Steve Liebowitz, Group Director, Global Regulatory Sciences - CMC
Cathy Ku, Director, Director, Global Regulatory Sciences - CMC
Gerry DiDonato, Associate Director, Global Regulatory Sciences - CMC, Saxagliptin Project Manager

BACKGROUND:

This meeting is a follow-up to the August 14, 2006, meeting regarding participation in the CMC pilot program for saxagliptin tablets (IND 63,634). BMS's upcoming NDA was accepted into the CMC pilot program on October 20, 2006, and is expected to be submitted January 2008. This meeting was requested on March 1, 2007, and granted on March 15, 2007. The purpose of this meeting was to brief the review team on the quality-by-design (QbD) aspects of the drug development of this tablet. The briefing package dated April 11, 2007, was received on April 12, 2007

THE MEETING:

FDA introduced the members of the CMC review team that will be responsible for reviewing the upcoming Saxagliptin NDA: Su Tran (lead), Prafull Shiromani, and Sharmista Chatterjee. Zi Qiang Gu from the Office of Compliance was also present at the meeting and is part of the larger review/inspection team. As the NDA submission date draws near, a field investigator will be identified and will also become part of the review/inspection team. Amy Bertha will be the CMC contact from the FDA for this pilot NDA.

BMS presented an updated version of the slides that were provided in the briefing package (an updated version of the slides are attached). During the presentation clarification questions were asked and discussions followed. Highlights from the clarification questions have been captured below.

In reference to the graph on slide 7, FDA asked what the difference between a Non-CPP III and Non-CPP IV was. BMS replied that a Non-CPP IV is a process parameter that has more inherent variability than a Non-CPP III. A Non-CPP III is more tightly controlled.

With reference to slide 14, FDA asked how the model compound metformin compared to saxagliptin in their coating operations. BMS commented that they have adequate data in-house to show that metformin behaves similarly to saxagliptin in solubility and thus has a similar response in the coating process.

In reference to the characterization profile graph on slide 15, FDA asked if the graph was referring to the C) BMS confirmed that it was.

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topic was being discussed at the ICH level. FDA asked BMS to provide their definitions of terms in the NDA.

Minutes Preparer: *Amy Bertha*

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment

Chair Concurrence: *Moheb Nasr*

Moheb Nasr, Ph.D.
Deputy Director
Office of New Drug Quality Assessment

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/s/

Chi Wan Chen
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,634

Bristol-Myers Squibb
Attention: Pamela J. Smith, M.D.
Director, Metabolic/Endocrine Products
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Smith:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-477118 C J b(4)

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on July 27, 2005. The purpose of the meeting was to discuss the nonclinical and clinical drug development program for saxagliptin.

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) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of minutes from the End-of-Phase 2 meeting held on July 27, 2005

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 27, 2005
TIME: 11:00 am to 12:00 pm
LOCATION: Parklawn Building, *Potomac Room*
APPLICATION: IND 63,634
DRUG NAME: Saxagliptin [BMS-447118] - **b(4)**
TYPE OF MEETING: Type B; End-of-Phase 2

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Lina AlJuburi, Pharm.D., M.S.

FDA ATTENDEES: (Title and Office/Division)

David Orloff, M.D.	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Robert Misbin, M.D.	Clinical Reviewer
Jeri El Hage, Ph.D.	Pharmacology/Toxicology Team Leader
John Colerangle, Ph.D.	Pharmacology/Toxicology Reviewer
Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
J. Todd Sahlroot, Ph.D.	Statistics Team Leader
Lee-Ping Pian, Ph.D.	Statistics Reviewer
Joslyn Swann, Pharm.D.	Safety Evaluator, Office of Drug Safety
Lina AlJuburi, Pharm.D.	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Bristol-Myers Squibb

Rex Parker, Ph.D.	Director, Metabolic and Cardiovascular Discovery Biology
Thomas J. Davidson, Ph.D.	Executive Director, Drug Safety
David W. Boulton, Ph.D.	Principal Research Scientist, Clinical Discovery
Robert Wolf, M.D.	Executive Director, Cardiovascular, Global Clinical Research, Saxagliptin Development Lead
Mary Beth Blauwet, Dr.PH.	Associate Director, Clinical Biostatistics
Pamela J. Smith, M.D.	Group Director, Regulatory Sciences, Metabolic/Endocrine Products
Margo Herron	Director, Regulatory Affairs, Regulatory Relations and Policy
Edith Wolff	Associate Director, Project Planning and Management
Angelina Trujillo M.D.	Director, Global Clinical Research
Kannan Natarajan Ph.D.	Group Director, Clinical Biostatistics
Junaideen Fahumy M.D.	Global Pharmacovigilance
Marc Thibonnier M.D.	Vice President Global Clinical Research, Metabolic Diseases
James List MD Ph.D.	Associate Director, Global Clinical Research, Metabolic Diseases

BACKGROUND:

IND 63,634 for saxagliptin (BMS-477118) was submitted on November 8, 2001. Saxagliptin is a dipeptidyl-peptidase IV (DPP-IV) inhibitor. This drug is being studied for monotherapy, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is also being studied for combination therapy, with either metformin, a thiazolidinedione or a sulfonylurea to further improve glycemic control in adults with type 2 diabetes mellitus whose hyperglycemia is inadequately controlled on either metformin, a thiazolidinedione or a sulfonylurea alone. In Phase 3 of the drug development program, the sponsor plans to study once daily doses of 1, 2.5, 5 and 10 mg.

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Proposed Phase 3 Studies

Monotherapy

Study CV181011 (Treatment-Naïve Diabetic Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise.*

Study CV18038 (Treatment-Naïve Diabetic Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise.*

Combination Therapy

Study CV181014 (Metformin Failure Subjects): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.*

Study CV181013 (Saxagliptin Combination with Thiazolidinedione): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Thiazolidinedione Therapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Thiazolidinedione Therapy Alone.*

Study CV181040 (Saxagliptin Add-On Prior to Titration of Sulfonylurea): *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Glyburide in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Glyburide Alone.*

Study CV181039 (Initial Combination Therapy for Treatment-Naïve Subjects with Type 2 Diabetes Mellitus): *A Multicenter, Randomized, Double-Blind, Active Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin XR as Initial Therapy versus Saxagliptin Monotherapy and Metformin XR Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Diet and Exercise.*

The sponsor requested this Type B End-of-Phase 2 meeting on May 11, 2005, and the background package was submitted on June 27, 2005.

MEETING OBJECTIVES:

To discuss the nonclinical and clinical drug development program for saxagliptin.

DISCUSSION POINTS:

Nonclinical Safety Assessment

- 1) Does the Agency agree that results of completed chronic toxicity studies (6 and 12 months in rats and 12 months in dogs) and the 1-month rat study with the active metabolite (BMS-510849) support dosing in clinical studies for more than 12 months at the doses selected for the Phase 3 program (2.5, 5, and 10 mg)?

Yes.

Clinical Pharmacokinetics, Drug Metabolism, and Clinical Pharmacology

- 2) Does the Agency agree that nonclinical studies and Phase 1 and Phase 2 data evaluating effects of saxagliptin on QTc intervals, as well as the planned thorough QTc study in healthy subjects, will provide sufficient characterization of the safety of saxagliptin with respect to QTc interval effects?

Yes.

- 3) The Clinical Pharmacology program includes: a) single and multiple ascending dose studies; b) a study to further assess the effects of saxagliptin on lymphocytes and assess cyanide formation from saxagliptin; c) a ¹⁴C-ADME study; d) completed drug-drug interaction studies with ketoconazole and metformin and planned studies with glyburide (a sulfonylurea), pioglitazone (a thiazolidinedione), digoxin (a P-gp substrate), and simvastatin (an HMG CoA reductase inhibitor that is a CYP3A4 substrate); e) a thorough QTc study; f) studies characterizing the pharmacokinetics of saxagliptin and its active metabolite, BMS-510849, in special populations (age and gender, renal impairment, hepatic impairment); g) a food effect study; h) 2 relative bioavailability studies for capsule vs. tablet formulations; i) population pharmacokinetic/pharmacodynamic analysis; j) studies to support new formulations, if required.

Does the Agency agree that the Clinical Pharmacology program will be adequate to support the Phase 3 program and the NDA filing and registration of saxagliptin? (See also Clinical Safety Question 10).

The sponsor needs to conduct an *in vitro* drug metabolism induction study. This should be an induction study with human hepatocytes from three donors with the appropriate positive control to study parent drug and metabolite. If the results indicate that there is no induction, then an *in vivo* drug metabolism study will not be necessary. Please refer to the guidance for industry document, entitled *Drug Metabolism/Drug Interaction*

Studies in the Drug Development Process: Studies In Vitro
(<http://www.fda.gov/cder/guidance/clin3.pdf>).

Phase 3 Program

Dose Selection

- 4) Based on preclinical pharmacology and toxicity studies and safety and efficacy results of Phase 1 and Phase 2 studies, does the Agency agree with the selection of once daily doses of 2.5, 5, and 10 mg of saxagliptin as well as the additional efficacy evaluation of a 1 mg dose in monotherapy study CV181038 to be studied in the Phase 3 program?

This appears to be acceptable.

Saxagliptin as Monotherapy for Treatment of Hyperglycemia

- 5) Does the Agency agree that outlines for the two monotherapy studies (CV181011 and CV181038), as proposed with respect to sample size, number of arms, primary and secondary endpoints, duration, patient population, inclusion/ exclusion/ discontinuation/ rescue and titration criteria, and biostatistical approach, will support the proposed indication for monotherapy of hyperglycemia in subjects with type 2 diabetes mellitus?

One Phase 3 monotherapy clinical trial should be sufficient. Two have been presented in the meeting briefing document: CV181011 and CV181038. Study CV181038 should be adequate, because it includes the 1 mg loose dose and the titration extension. The titration-to-goal design for the extension study mimics real world practice. However, the Division welcomes further discussion on this topic.

For patients requiring rescue, the last value before rescue therapy should be used in the statistical analyses. Please include in the intent-to-treat (ITT) analysis population all patients who have any exposure to drug and any post-randomization HbA1c data prior to rescue. The sponsor should do a sensitivity analysis restricting the population to those patients with 4weeks or more of exposure.

The Division suggests you consider adding region or country as an additional term in the primary statistical model. The preference is for region.

Saxagliptin Combination Therapy for Treatment of Hyperglycemia

- 6) Does the Agency agree that the combination therapy studies (CV181014, CV181013, CV181039 and CV181040), as proposed with respect to sample size, number of arms, primary and secondary endpoints, duration, patient population, inclusion/ exclusion/ discontinuation/ rescue and titration criteria, and biostatistical approach, will support the proposed indications for second-line (add-on) combination therapy of saxagliptin with metformin, or with a TZD, or with a sulfonylurea, and for first-line (initial) combination therapy of saxagliptin with metformin for the treatment of hyperglycemia in subjects with type 2 diabetes mellitus?

When designing the clinical development program for combination therapy as first-line, the sponsor needs to be certain that the two drugs are better than either one alone. The added benefit without additional risk of starting two drugs instead of one will need to be demonstrated. Additional pharmacokinetic and/or pharmacodynamic risks with the combination also need to be explored and addressed.

Durability of Efficacy of Saxagliptin as Monotherapy and Combination Therapy

- 7) Does the Agency agree that the extensions planned for the monotherapy and combination therapy studies will provide sufficient data on durability of efficacy effect of saxagliptin in monotherapy and in add-on and initial combination therapy of saxagliptin with oral antidiabetic agents (metformin, TZD, or sulfonylurea) to include description of these results along with the results for primary and secondary endpoints in the Clinical Studies section of the label?

This proposal appears to be acceptable.

Clinical Safety in Phase 3

- 8) Does the Agency agree with the proposed approach to the assessment of the effects of saxagliptin (in the presence and absence of ketoconazole) on absolute lymphocyte counts and any associated clinical signs and symptoms with respect to:
- Ongoing and anticipated studies characterizing the etiology and clinical significance of the adverse clinical (transient fever and/or flu-like symptoms) and laboratory (transiently decreased lymphocytes) experiences in the initial ketoconazole and metformin interaction studies?
 - The exclusion/ inclusion criteria in the proposed Phase 3 studies?
 - Doses selected for Phase 3?

The proposal in regard to lymphocyte counts appears to be acceptable.

- 9) Does the Agency agree with the proposed Phase 3 Safety Monitoring Plans with respect to:
- Hematological and immunologic safety algorithms?
 - Hypoglycemia algorithm?
 - Inclusion/Exclusion/Discontinuation parameters for hepatic, musculoskeletal, cardiovascular, and renal safety?
 - External Data Monitoring Committee?

The proposal for the planned Phase 3 safety monitoring appears to be acceptable.

Pediatric Patients

- 10) Does the Agency agree to defer the submission of data on pediatric patients until after submission of the original NDA?

The Division agrees that pediatric studies should not be initiated until the safety profile of saxagliptin is characterized in adults. Therefore, the sponsor's request for a deferral of pediatric studies will be granted.

Total Clinical Exposure in the Saxagliptin Development Program

- 11) Does the Agency agree that the proposed clinical exposure database to be submitted in the original NDA and the 4-month safety update documenting the safety of saxagliptin for the number of subjects treated for 6, 12, and 18 months will be sufficient for registration of saxagliptin for the treatment of hyperglycemia in subjects with type 2 diabetes mellitus?

The clinical exposure database appears to be acceptable.

Mechanism of Action of Saxagliptin

- 12) With respect to BMS plans to develop exploratory clinical studies designed to characterize the mechanism of action of saxagliptin on β -cell function, secretory capacity, and insulin sensitivity, the Sponsor proposes to use several surrogate measures of pancreatic β -cell function (homeostatic model of assessment and oral glucose tolerance test, frequent-sampling oral, and possibly intravenous, tolerance test, arginine stimulation test, and clamp studies).

Does the Agency regard any one or more of the proposed surrogate measures as particularly valuable and appropriate approaches for exploratory assessment of the potential for saxagliptin to preserve and enhance pancreatic β -cell function and secretory capacity in these studies?

Any claim related to preservation of beta-cell function must be supported by data that define an actual clinical benefit associated with the biochemical evidence.

Future Indications

Durability and Disease Progression Trial

- 13) With respect to BMS plans to develop clinical studies designed to evaluate the long-term durability of effect of saxagliptin and its efficacy in prevention or delay of disease progression, or of regression of disease, what Regulatory requirements does the Agency anticipate with respect to critical trial design features, e.g. efficacy endpoints, duration, and patient population?

Refer to the response to question 14.

Disease Prevention

14) Prevention or delay of type 2 diabetes mellitus is a potentially important therapeutic target. Because of the possible benefits of incretin augmentation on the preservation of β -cell function and insulin secretory capacity, saxagliptin may be a suitable candidate for study of its safety and efficacy in the prevention or delay of diabetes in high-risk populations. What regulatory requirements does the Agency anticipate for future indications for prevention/delay of type 2 diabetes mellitus with respect to:

- Target populations?
- Safety profile?
- Sample sizes?
- Study duration?
- Endpoints/ Outcomes/ Surrogate measures?
- Need for terminal treatment washout?

The use of an agent proven effective in the treatment of an existing clinical condition for the prevention of that condition requires that risk versus benefit be re-defined in the new population. In the simplest analysis, it must be remembered that the “prevention” population is relatively healthy in comparison to the “treatment” population. The absolute risk of diabetes and of its sequelae in the target population must therefore be considered, as this is obviously the determinant of the maximum absolute benefit of the intervention against which any risks will be weighed. With regard to sample size, aside from what is necessary to define extent of expected benefit, whether or not safety can be extrapolated from experience in the “treatment” population will dictate in part the size of the safety exposures necessary. Study duration must not only be adequate to assess long-term safety but also to assess the durability of any preventive effect of the drug. Time to diagnosis of diabetes is the endpoint of primary interest, with other metabolic parameters related to diabetes or risk thereof also important. Washout with follow up glucose tolerance testing may serve multiple purposes in the final work up of potential drug effects. First, were a product hypothesized to have effects to permanently arrest the progression to diabetes, a washout would be needed to establish this fact. For a product intended for lifelong use, a washout (or randomized withdrawal of treatment) could be considered in order to establish the continued necessity of treatment. Additionally, a washout might be considered in order to elucidate the mechanism of diabetes “prevention” of a given agent.

Minutes Preparer: Lina AlJuburi
Chair Concurrence: David Orloff

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/s/

Lina Aljuburi
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