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
ılation 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

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rom: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Thursday, June 04, 2009 5:27 PM
To: 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 tha' 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

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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

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Hartford, Rachel

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:o: 'Smith, Pamela'
Subject: RE: saxagliptin

Good Afternoon Pam,

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Thank you,

Rachel

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Subject: RE: saxagliptin

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