

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-350

STATISTICAL REVIEW(S)

MEMORANDUM OF CONSULTATION

Date: June 25, 2009

Between:

Saxagliptin review team
and
Joy D. Mele, M.S. (DB2)

Subject: Response of patients titrated from 2.5 mg to 5.0 mg in Study 38 (NDA 22-350)

In the wrap-up meeting for saxagliptin, the lack of dose response across the doses of 2.5 mg to 10 mg was discussed. Because of concerns regarding the increased exposure for saxagliptin with co-administration with ketoconazole, the question of whether the 5 mg dose offers any advantage over the 2.5 mg dose arose. The data from one treatment arm in Study 38 where patients were titrated from 2.5 mg to 5.0 mg based on response may offer some insight as to the benefit of having the dose of 5.0 mg available.

The following (extracted from Section 3.1.2 of the Study 38 report) briefly summarizes the treatment groups and the criteria for titration.

Subjects were randomized (1:1:1:1:1) to 1 of 5 treatment groups: saxagliptin 2.5 mg QAM, saxagliptin 2.5 mg with possible titration to 5 mg QAM (2.5/5 mg QAM), saxagliptin 5 mg QAM, saxagliptin 5 mg QPM, or placebo. In subjects who were randomized to the saxagliptin 2.5/5 mg QAM treatment group, saxagliptin was initiated at 2.5 mg and titrated to 5 mg based on criteria shown in Table 3.1.2A.

Table 3.1.2A: Titration Criteria

Visit	Mean Fasting Plasma Glucose (MFPG) ^a	Mean Fasting Whole Blood Glucose (MFWBG) ^a
Week 4	≥ 150 mg/dL (8.3 mmol/L)	≥ 140 mg/dL (7.7 mmol/L)
Week 8	≥ 140 mg/dL (7.7 mmol/L) and ≤ 220 mg/dL (12.2 mmol/L)	≥ 131 mg/dL (7.2 mmol/L) and ≤ 203 mg/dL (11.3 mmol/L)
Weeks 12 and 24	≥ 126 mg/dL (7.0 mmol/L) and ≤ 200 mg/dL (11.1 mmol/L)	≥ 118 mg/dL (6.5 mmol/L) and ≤ 185 mg/dL (10.3 mmol/L)

Source: Appendix 1.1

^a The calculation of mean fasting glucose (MFG) was based on fingerstick data from subject self blood glucose monitoring for at least 3 of the 5 days preceding the visit.

A total of 71 patients were randomized to the titration group and 73% completed the 24 week treatment period.

Table 3.1.1.10 Study 38 Reasons for discontinuation during 24-week period for patients randomized and treated

	Placebo n=74	2.5AM n=74	2.5tAM n=71	5AM n=74	5PM n=72
Rescued	11 (15%)	8 (11%)	9 (13%)	10 (14%)	8 (11%)
ADE	1 (1%)	0	2 (3%)	0	1 (1%)
Pt request	4 (5%)	4 (5%)	1 (1%)	4 (5%)	5 (7%)
Lost-to-follow-up	3 (4%)	4 (5%)	2 (3%)	2 (3%)	3 (4%)
Other	1 (1%)	3 (4%)	4 (6%)	1 (1%)	0
Completed 24 weeks	53 (72%)	55 (74%)	52 (73%)	57 (77%)	55 (76%)

Numbers extracted from applicant's study report.

Of the 71 patients randomized to the titration arm, 56 (79%) were titrated from 2.5 mg to 5.0 mg based on the titration criteria shown on the previous page. The median time to titration was 54 days (~8 weeks); only 2 patients were titrated within the first month of treatment. Using the dataset DOSING, I identified 53 patients with dosing titrated to 5 mg during the 24 week treatment period.

The sponsor states the following in their discussion although this reviewer could find no efficacy results that specifically addressed this issue by the sponsor.

There did not appear to be any advantage to titration from 2.5 to 5 mg compared to the fixed dose treatment groups, because there was neither additional efficacy nor avoidance of hypoglycemia or other tolerability or adverse event findings with titration.

To look at whether patients improved their effect with titration I looked at the change from baseline in HbA1c prior to titration compared to the change in HbA1c when titrating from the 2.5 mg dose to the 5 mg dose. The paired difference (change on 5 mg minus change on 2.5 mg) indicates on average a larger change on 5 mg than on the 2.5 mg dose (-0.18) and the difference is borderline significant with p=0.07. (See Figures 1 and 2 on the following page that show the data for individual patients.)

Table 1. Changes in HbA1c for those patients who had their dose titrated from 2.5 mg to 5.0 mg (N=53)

	Mean (SD)
Change from baseline on 2.5 mg dose	-0.45 (0.8)
Change from baseline on 5.0 mg dose	
Baseline is last value on 2.5 mg	-0.18 (0.65)
Baseline is original baseline at Visit 0	-0.67 (1.1)
Change from original baseline at last visit on 5 mg minus change from original baseline at last visit on 2.5 mg	-0.18 (0.65)
Paired Difference	p=0.07
Paired t-test result	

This data does not provide evidence of a dose response for saxagliptin for 5 mg over 2.5 mg; dose response is assessed in studies where patients are randomized to dose (e.g. Study 011). The analysis here is on a subset of patients for whom the 2.5 mg dose was not considered effective based on titration criteria provided in the protocol. This data does suggest that for some patients who do not respond to 2.5 mg dose, a benefit may be afforded by increasing the dose to 5.0 mg.

Figure 1 For patients with dose titrated from 2.5 mg to 5 mg during 24 week treatment period, last hba1c value on 2.5 mg dose versus last HbA1c on 5.0 mg dose. Values under the identity line indicate lower HbA1c's on the 5 mg dose compared to the 2.5 mg dose

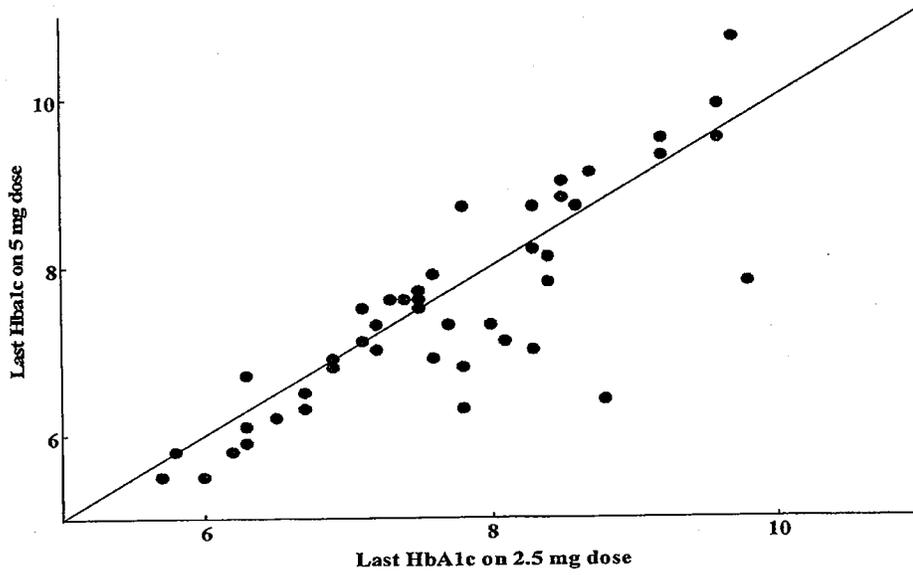
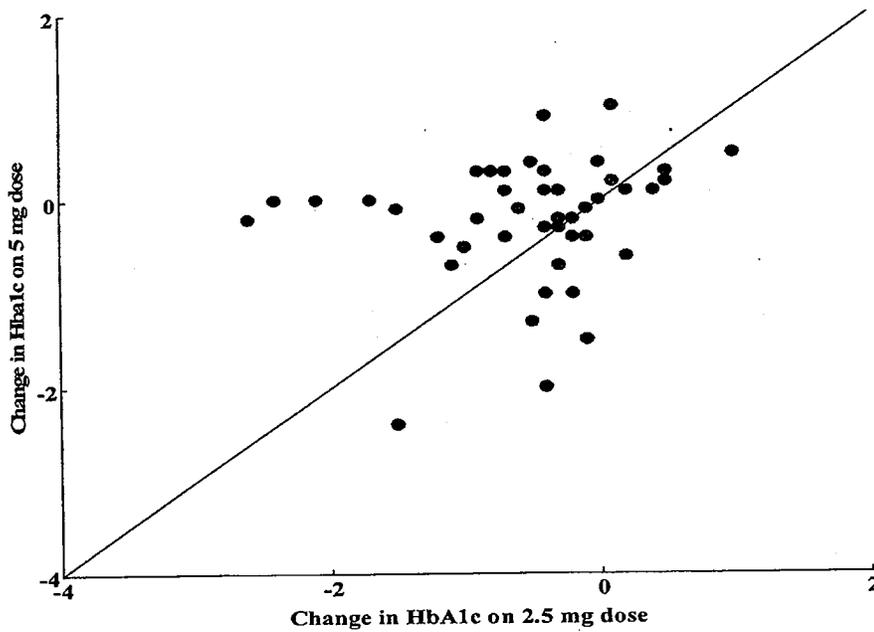


Figure 2 For patients with does titrated from 2.5 mg to 5 mg during 24 week treatment period, change from baseline (Week 0) to last HbA1c on 2.5 mg dose versus change from baseline (Last week on 2.5 mg dose) to last HbA1c on 5.0 mg dose. Values under the identity line indicate larger changes on the 5 mg dose



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/s/

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-350 /0000

Drug Name: Saxagliptin (tablets of 2.5 and 5.0 mg)

Indication(s): Type 2 Diabetes Mellitus

Applicant: Bristol-Myers Squibb Company

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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

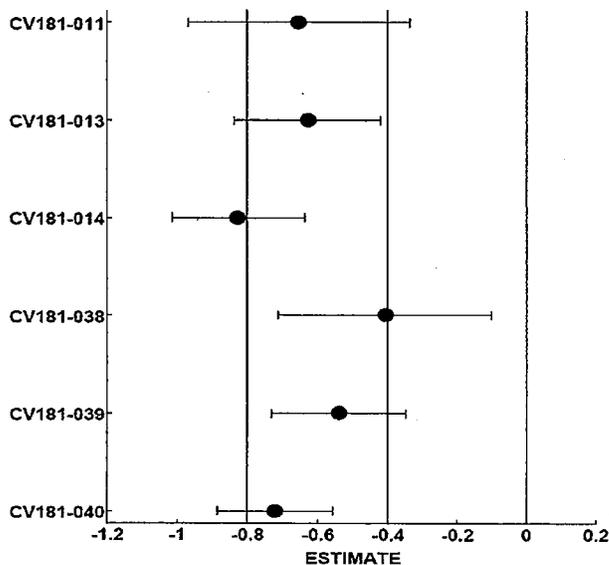
1.1 Conclusions and Recommendations

The applicant has submitted the results of eight clinical trials to support the efficacy and safety of saxagliptin for the treatment of Type 2 diabetes; six of these trials are Phase 3 clinical trials. These double-blind, randomized trials had several design features in common: a single-blind run-in period, a 24-week treatment period for assessing efficacy based on changes in HbA1c, an extension period of 12 or more months. The purpose of the extension period was to assess safety long-term. To enter this period, patients who were rescued with open-label therapy due to a lack of glycemic control were continued on double-blind treatment along with patients who completed the 24-week short-term period. For this review which primarily reports the efficacy findings, the focus is the data from the 24-week short-term period.

Two monotherapy studies provided data for assessing dose response; in Study 8, doses from 2.5 to 40 mg were compared to placebo while in Study 11, doses of 2.5, 5 and 10 were studied against placebo. Two other studies (Studies 14 and 39) included doses up to 10 mg in combination with metformin. No studies showed a dose response (see Figures 3.1.1.1 and 3.1.1.5); all studies showed statistically significant treatment effects for all doses of saxagliptin compared to placebo. One study (Study 39) contained both a metformin monotherapy arm and a saxagliptin 10 mg monotherapy arm; a comparison of these arms showed a decrease of 0.3 greater for metformin than saxagliptin. The applicant has chosen the dose of 5 mg for marketing with the 2.5 mg dose available for some special populations arguing that the 10 mg dose does not provide additional benefit and the 5 mg dose has a comparable safety profile to the 2.5 mg dose.

In addition to being studied as monotherapy, three trials examined the benefit of adding saxagliptin to an oral antidiabetic medication (TZD, metformin or glipizide) in patients inadequately treated on these medications. Another trial examined the efficacy and safety of saxagliptin and metformin in combination as initial therapy in patients naïve to antidiabetic treatment. In all four studies, statistically significant treatment effects were seen for all doses of saxagliptin studied.

Figure 1.1.1 HbA1c change from baseline Week 24 LOCF treatment difference for saxagliptin 5 mg versus placebo



The treatment differences for all 6 trials comparing saxagliptin 5 mg to placebo (Figure 1.1.1) show results favorable to saxagliptin ranging from -0.8 to -0.4; with five of the trials producing decreases of 0.5 or greater.

High rates of rescue due to lack of glycemic control were generally associated with larger treatment differences for placebo versus saxagliptin (see Section 3.1.4). For most studies, rescue rates were higher for placebo patients than saxagliptin patients although this was not true in all studies and also there was no dose response regarding rescue. Notably higher rates of rescue were seen in USA sites than non-USA sites. In addition, the probability of rescue was increased with increased baseline HbA1c, FPG and BMI regardless of treatment. The implications of these findings for future trials should be examined. For example, the impact of stringent rescue criteria on rescue rates and, in turn, on the estimation of the treatment effect should be studied for differing designs which would help in the interpretation of future results. This reviewer believes the estimates computed for the saxagliptin trials are acceptable but that the difficulty arises when one interprets the estimates in the context of results for other products where trial designs may differ in ways that influence the magnitude of the effect.

In Study 39, a study of initial therapy with combination metformin and saxagliptin in naïve patients, the rescue rate in the monotherapy saxagliptin arm was notably high at 40%, about 20% higher than the rates seen in the other 3 treatment arms. This lack of efficacy is concerning given that Study 39 was a study of naïve patients with high baseline values (mean of about 9.5) and that saxagliptin was administered at the high dose of 10 mg. Considering also that, in general, high baseline HbA1c values are associated with high rescue (see Table 3.1.15), the efficacy of saxagliptin for these patients is clearly marginal.

Subgroup analyses based on gender, age, race, baseline HbA1c, and USA/non-USA revealed the following significant interactions:

- A larger treatment effect was seen for males than females in the large monotherapy study (Study 11, $p=0.01$) which was not replicated in other studies.
- Highly significant interaction ($p=0.008$) based on race in Study 39 showed Asians with the largest effect. This finding suggests that PK exposure should be studied and consideration given to assessing important safety findings in this subgroup.

This reviewer concludes that the applicant has adequately shown saxagliptin to be effective at lowering HbA1c based on six Phase 3 trials. Recommendations regarding the reporting of the efficacy in labeling are given in the last section of this review.

1.2 Brief Overview of Clinical Studies

Saxagliptin, a new chemical entity, is a dipeptidyl peptidase-IV (DPP-IV) inhibitor which augments postprandial insulin secretion. It has been studied in 10 Phase 2/3 trials. Studies CV181054, CV181056 and CV181062 are ongoing trials for which no study reports or data have been submitted and therefore are not reviewed here. The trials shown in the grayed area of Table 1.2.1 (all of which are described in the applicant's proposed labeling) are reviewed in this document in detail; a brief summary of Study CV181008 is provided. Study CV181041, a small study of 36 patients designed to assess mechanism of action, is not reviewed here.

Table 1.2.1 Randomized, double-blind clinical trials designed to assess safety and efficacy

Study (# of centers)	Special Design Features	Patient Population	Treatment Groups (N)	Duration of treatment
CV181008	Variable treatment period /2 cohorts	Drug-naïve	SAXA 2.5, 5, 10, 20, 40 and 100 Placebo	6 to 12 weeks
CV181011	Double-blind cohort and open -label cohort	Drug-naïve	SAXA 2.5, 5 and 10 Placebo	24 weeks 18 months+ LT ongoing
CV181013	OL TZD SAXA add-on	TZD failures	TZD+SAXA 2.5 TZD+SAXA 5 TZD+Placebo	24 weeks
CV181014	OL MET SAXA add-on	MET failures	MET+SAXA 2.5 MET+SAXA 5 MET+SAXA 10 MET+Placebo	24 weeks 12 months+ LT ongoing
CV181038	QPM and QAM dosing	Drug-naïve	SAXA 2.5 QAM SAXA 2.5→5 QAM SAXA 5 QAM SAXA 5 QPM Placebo QD	24 weeks 12 months+ LT ongoing
CV181039	Combination with metformin	Drug-naïve	SAXA 5+MET500 SAXA 10+MET500 SAXA 10 MET 500+	24 weeks 12 months+ LT ongoing
CV181040	OL Glyburide SAXA add-on	SU failure	GLY7.5+SAXA 2.5 GLY10+SAXA 5 GLY10+Placebo	24 weeks 12 months+ LT ongoing
CV181041	Mechanism of action Insulin secretion endpoints	Drug-naïve	SAXA 5 Placebo	12 weeks 24 months+ LT ongoing
CV181054	Glipizide control	Type 2 diabetics	MET+SAXA 5 MET+glipizide	52 weeks ONGOING no report
CV181056	sitagliptin control	Type 2 diabetics	MET+SAXA 5 MET+sitagliptin 100	18 weeks ONGOING no report
CV181062	low dose	Patients with renal impairment	SAXA 2.5 Placebo	12 weeks ONGOING no report

2. Introduction

2.1 Overview

See section 1.2

2.2 Data Sources

The applicant submitted electronic raw datasets (essentially CRF data) and derived datasets which can be accessed at this link; [\CDSESUB1\EVSPROD\NDA022350\0000](#). Additional disposition data was requested and was received November 3, 2008. Cardiovascular data was requested by FDA and received in January, 2009 in preparation for an advisory committee meeting on April 1, 2009.

The applicant's electronic submission was well-organized. Parallel structure in the presentation of the results across all studies was well-done and appreciated by the reviewer.

All graphs and tables in the review were created by this reviewer unless otherwise noted.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

This section provides results from 3 types of trials designed to establish the efficacy and safety of saxagliptin: monotherapy studies, add-on studies and a combination study.

The statistical methods for the Phase 3 trials were summarized by the applicant in a Core Statistical Analysis Plan. Specifics for the individual trials were included within each individual study report. In this section, this reviewer will briefly describe the Core Statistical Plan; specific comments for individual studies are included in the review sections below if important to the interpretation of the results.

The objective of all the Phase 3 trials was to show superiority of saxagliptin over control for change from baseline of HbA1c after 24 weeks of therapy.

The efficacy analysis population was composed of all patients who took at least one dose of double-blind treatment, who had a response value on treatment and who had a baseline value. The applicant's safety analysis population was a similar population but assigned patients to the treatment group that represented the therapy they received (which may not necessarily be the randomized treatment).

The primary analysis uses the last observed measurement at study completion, before dropout or rescue. The statistical model is an analysis of covariance (ANCOVA) model with baseline as a covariate. To test for equal slopes, the interaction of treatment and baseline is assessed. Several sensitivity analyses were planned. Secondary endpoints were to be tested sequentially to control the Type 1 error rate.

The incidence of rescue therapy was summarized with a Kaplan-meier curve and a reporting of the difference in proportions with confidence limits on the difference at several timepoints.

3.1.1 Monotherapy Trials

Three Phase 2/3 studies were designed to study saxagliptin as monotherapy treatment for Type 2 diabetes; Studies CV181008, CV181011 Type and CV18138 (henceforth referred to as Studies 08, 11 and 38, respectively [Table 3.1.1.1]). A fourth trial, CV181041, compared one dose, 5 mg, of saxagliptin to placebo in a 12 week mechanism of action study; this trial is not reviewed here but is included in the safety database. Study 08 is a Phase 2 study only briefly reviewed here while the other two studies, 11 and 38, are Phase 3 studies that are fully reviewed in subsequent sections.

Table 3.1.1.1 Randomized, double-blind clinical trials monotherapy

Study (# of centers)	Special Design Features	Patient Population	Treatment Groups (N)	Duration of treatment
CV181008	Variable treatment period ; two cohorts	Drug-naïve	SAXA 2.5, 5, 10, 20, 40 and 100 Placebo	6 to 12 weeks
CV181011	Double-blind cohort and open -label cohort	Drug-naïve	SAXA 2.5, 5 and 10 Placebo	24 weeks 18 months+ LT ongoing
CV181038	QPM and QAM dosing	Drug-naïve	SAXA 2.5 QAM SAXA 2.5→5 QAM SAXA 5 QAM SAXA 5 QPM Placebo QD	24 weeks 12 months+ LT ongoing
CV181041	Mechanism of action Insulin secretion endpoints	Drug-naïve	SAXA 5 Placebo	12 weeks 24 months+ LT ongoing

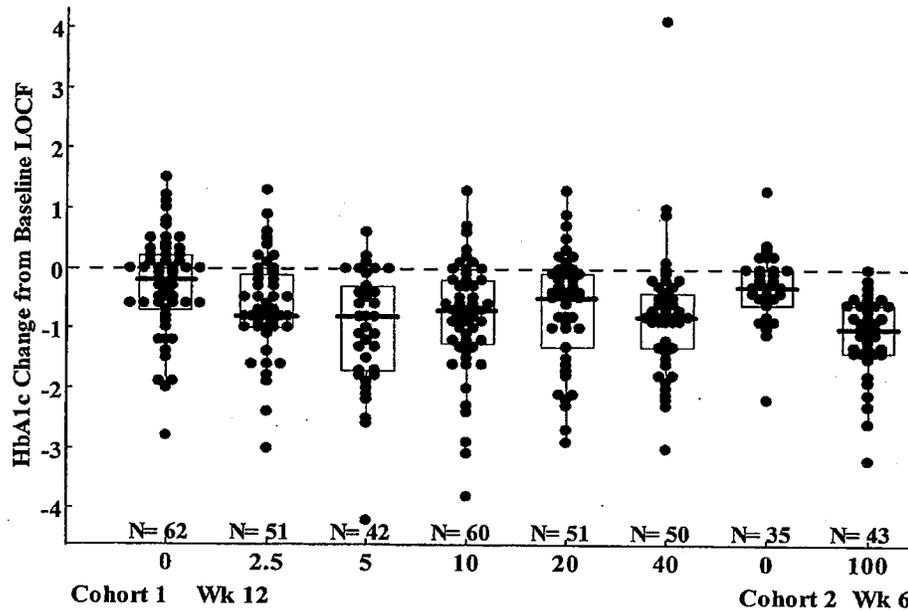
Study 08

Study 08 is a Phase 2, multicenter, randomized, parallel-group, placebo-controlled, proof of concept study designed to examine the change in HbA1c over a range of doses (0, 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg). The protocol was amended 6 months into the trial with Amendment 4 which allowed for randomization of additional patients to a 100 mg dose group of saxagliptin and a second placebo group. A total of 338 (316 with HbA1c data) patients randomized to doses 0 to 40 under the original protocol were followed for a maximum of 12 weeks while 85 (78 with HbA1c data) patients randomized to placebo or 100, under Amendment 4, were followed for a maximum of 6 weeks. About 83% of the patients completed 12 weeks in the original cohort and 93% completed 6 weeks in the Amendment 4 cohort. These two groups of patients were analyzed separately by the applicant.

For the original cohort of doses 0 to 40, the applicant reported no evidence of dose response (ANCOVA model with test for log linear trend, $p > 0.9$, reviewer's Figure 3.1.1.1.) and statistically significant differences for each dose versus placebo ($p < 0.012$, Dunnett's multiple comparisons test) with treatment effects over placebo of 0.4% or greater. This reviewer confirmed the applicant's findings. For the Amendment 4 cohort, the applicant reported a statistically significant treatment effect of about 0.6% for the

100 mg dose over placebo.

Figure 3.1.1.1 Change from baseline HbA1c at endpoint (last-observation-carried-forward) by treatment group



In Section 13 of the study report, the applicant states “*In this study, the safety and tolerability profile for all doses of BMS-477118 was similar to placebo.*” However, the Overall Conclusions (Section 14) state that “*The safety and tolerability profile was comparable to that of placebo at doses of BMS-477118 below 20 mg.*” The safety data presented for Study 08 supports the former statement and not the latter statement. Overall, Study 08 showed no dose response for either efficacy or safety suggesting that the low doses may be sufficient for achieving the optimum benefit from saxagliptin. The number of patients studied at 100 mg is too small to draw definitive conclusions about this high dose with regard to safety.

Study 11

Design

Study 11 is a double-blind, randomized trial designed to assess the efficacy and safety of three doses of saxagliptin compared to placebo. After a 2-week placebo lead-in, patients satisfying entry criteria were randomized, stratifying on site, to placebo or to doses of 2.5, 5 or 10 of saxagliptin and followed for up to 24 weeks. Medication was to be taken daily prior to the morning meal. Patients who completed the 24 weeks of double-blind treatment and patients who were rescued before Week 24 were followed into a long-term period of an additional 42 months where double-blind randomized treatment was continued. The primary goal of the extension was to assess safety and tolerability although glycemic parameters continued to be measured. The focus for assessing efficacy is the initial 24-week period.

The primary outcome variable in this trial was HbA1c at Week 24 or endpoint (last-observation-carried-forward before rescue). HbA1c was measured at screening, baseline, Weeks 4, 6, 8, 12, 16, 20 and 24. Secondary outcomes were fasting plasma glucose (FPG), proportion of subjects achieving HbA1c<7% and AUC from 0 to 180 minutes for PPG response to an OGTT.

Entry criteria included the following:

- $7\% \leq \text{screening HbA1c} \leq 10\%$
- Naïve to anti-hyperglycemic therapy
- No significant cardiovascular history; no CHF Stage III or IV
- No active liver disease

Based on the rescue criteria listed below in Table 3.1.1.2, patients were eligible for open-label add-on metformin therapy and were followed into the long-term phase of the trial. Their last measurement of HbA1c before rescue was used to assess the primary endpoint. No changes in blinded medication were made at the time of rescue or at any time during the extension phase; the blind was not broken for the long-term extension.

Table 3.1.1.2 Study 11 Rescue criteria (Table 3.1.2 in the applicant's study report)

Short Term Visit	Fasting Plasma Glucose (FPG) (central laboratory)
Weeks 4 and 6	FPG > 240 mg/dL (13.3 mmol/L)
Week 8	FPG > 220 mg/dL (12.3 mmol/L)
Weeks 12, 16, 20, 24	FPG > 200 mg/dL (11.2 mmol/L)

Rescue during the long-term extension was based on HbA1c levels. Patients not controlled by the addition and titration of metformin during either the short-term or long-term phases were to be discontinued from the trial.

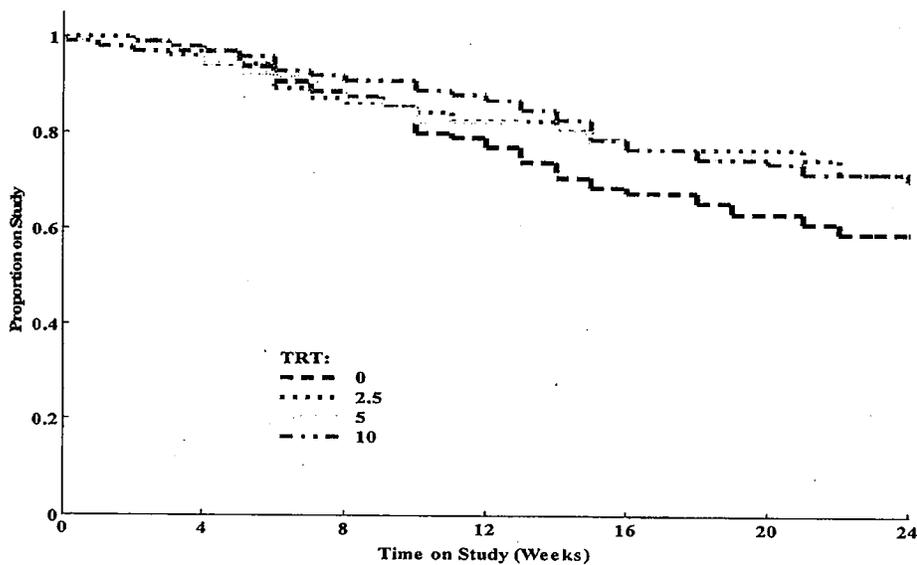
Patient Disposition

A total of 403 patients were randomized into 4 treatment groups (Table 3.1.1.3); two patients were not treated and are not included in any analyses. Eleven treated patients discontinued on the day of randomization and are not included in the ITT population for efficacy. The majority of the sites randomized less than 2% of the overall patients; the exceptions were a Mexican site (#145) with 6% and a US site (#48) with 3.5%. About half the patients were randomized in US sites (see Table 3.1.1.4 for a breakdown by country). Less than 70% of the patients completed 24 weeks with the lowest completion rate seen for placebo (58%, Figure 3.1.1.2). These completion rates are consistent with what has been seen in other short-term diabetes trials within this class of anti-diabetic drugs and in other classes as well; for example, for rosiglitazone, completion rates for monotherapy trials in naïve patients was about 60% for placebo patients and about 78% for treated patients. Most of the patients that completed 24 weeks continued into the extension and all rescued patients entered the extension.

Table 3.1.1.3. Study 11 Patient Disposition

	Placebo	SAXA 2.5	SAXA 5	SAXA 10
Total Randomized	96	102	107	98
Randomized and Treated	95 (99%)	102 (100%)	106 (99%)	98 (100%)
Number (%) on Study				
Wk 8	84 (88%)	89 (87%)	96 (90%)	90 (92%)
Wk 12	75 (78%)	96 (94%)	87 (81%)	86 (88%)
Wk 16	65 (68%)	90 (88%)	83 (78%)	77 (79%)
Wk 20	60 (63%)	78 (76%)	78 (74%)	73 (74%)
Wk 24 Completers	55 (58%)	73 (72%)	68 (64%)	69 (70%)
ITT patient for efficacy	92 (96%)	100 (98%)	103 (96%)	95 (97%)
Continued into Extension				
Total	79 (83%)	87 (85%)	87 (82%)	83 (85%)
Not rescued by Wk 24	54 (56%)	73 (72%)	66 (62%)	69 (70%)
Rescued by Wk 24	25 (26%)	14 (14%)	21 (20%)	14 (14%)

Figure 3.1.1.2 Proportion of patients on study by week and treatment group



The primary reason for not completing 24 weeks of treatment (Table 3.1.1.4) in all treatment groups was being rescued based on FPG levels (see Table 3.1.1.2). Rescue can be thought of as a measure of the effectiveness of the randomized treatment if the criteria are systematically applied across the treatment groups. So the expectation is that more patients will be rescued in the placebo group than the saxagliptin group which is clearly the case (log rank test of all saxagliptin groups versus placebo, p=0.02). However it should be noted that there is no clear dose response with regard to rescue. No other significant treatment differences in reasons for dropout were seen either with regard to reason or timing of dropout.

Table 3.1.1.4. Study 11 Reasons for discontinuation during 24-week period for patients randomized and treated

	Placebo n=95	SAXA 2.5 n=102	SAXA 5 n=106	SAXA 10 n=98
Rescued	25 (26%)	14 (14%)	21 (20%)	14 (14%)
ADE	0	3 (3%)	3 (3%)	4 (4%)
Pt request	11 (12%)	9 (9%)	13 (12%)	5 (5%)
Lost-to-follow-up	4 (4%)	0	2 (2%)	3 (3%)
Prot. Viol.	1 (1%)	1 (1%)	1 (1%)	3 (3%)
Lack of efficacy	0	1 (1%)	0	0
Other	0	1 (1%)	0	0

Numbers computed based on variable dc_st in dataset tmdsc011 with decoding from the CRF.

Rescue is strongly related to baseline HbA1c and baseline FPG with greater numbers of rescues for baseline values above the median (Table 3.1.1.5). There is no evident dose response with the 5 mg dose showing the highest number of rescues among the three saxagliptin doses.

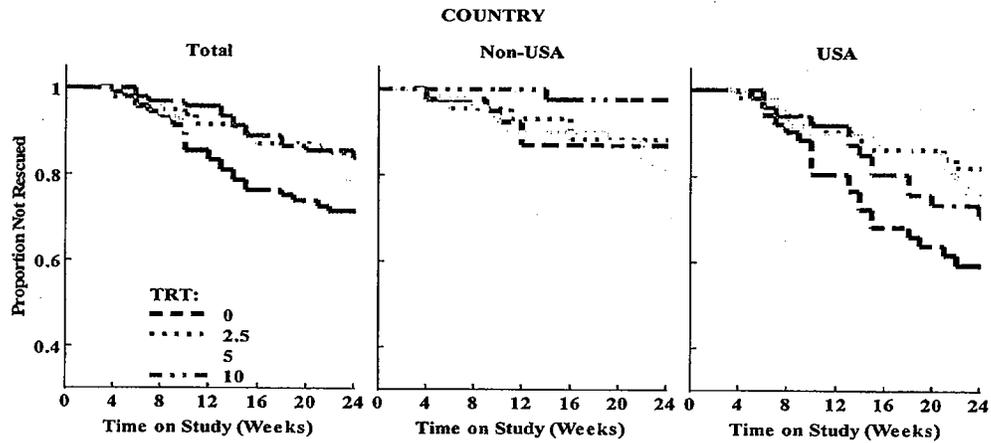
A logistic regression analysis by treatment group conducted by this reviewer yielded similar predictors for rescue across treatments. Baseline HbA1c, baseline FPG and baseline BMI were found to be the strongest predictors of rescue regardless of treatment group. HbA1c and FPG are correlated at baseline while BMI is not correlated with either of these 2 glycemic measures.

Table 3.1.1.5 Percent rescued by median baseline FPG, median baseline HbA1c and median baseline BMI for efficacy analysis population

	Placebo n=92	SAXA 2.5 n=100	SAXA 5 n=103	SAXA 10 n=95
Median baseline FPG				
<164	4/48 (8%)	0/45	1/50 (2%)	1/49 (2%)
≥164	21/44 (48%)	14/55 (25%)	20/53 (38%)	13/46 (28%)
Median baseline HbA1c				
< 7.7	5/49 (10%)	1/49 (2%)	0/48	2/46 (4%)
≥ 7.7	20/43 (47%)	13/51 (25%)	21/55 (38%)	12/49 (24%)
Median BMI				
< 31.5	14/57 (25%)	4/43 (9%)	6/48 (13%)	3/45 (7%)
≥ 31.5	11/35 (31%)	10/57 (17%)	15/55 (27%)	11/50 (22%)

The graph on the following page shows the proportion of patients not rescued for the total population and then broken down by non-USA sites (46% of patients) and USA sites (54% of patients). Two differences between the USA sites and the non-USA sites are apparent: 1) an overall higher rescue rate (~28%) is seen for the USA sites than the non-USA sites (~12%) and 2) for the recommended dose of 5 mg, a treatment difference favorable to saxagliptin is only seen for the USA sites. This data suggests that the efficacy data should be examined by USA/non-USA and that the rescue criteria may not have been applied comparably across sites.

Figure 3.1.1.3 Proportion of patients not rescued by week and treatment group



To check if there was evidence that rescue criteria were applied differentially across countries and sites, this reviewer looked at FPG levels overtime for rescued and non-rescued patients and found no clear evidence that patients were not rescued in non-USA sites when FPG values rose above the pre-defined FPG rescue criteria.

Comparing baseline values across countries, this reviewer found that baseline values for FPG and BMI for USA sites were higher than those seen in other countries. Considering that a relationship between these values and rescue was seen overall in analyses by this reviewer, it is likely that the differences in rescue seen for the USA sites versus the non-USA sites is based on differences in the populations on important predictors of rescue.

Baseline Demographics

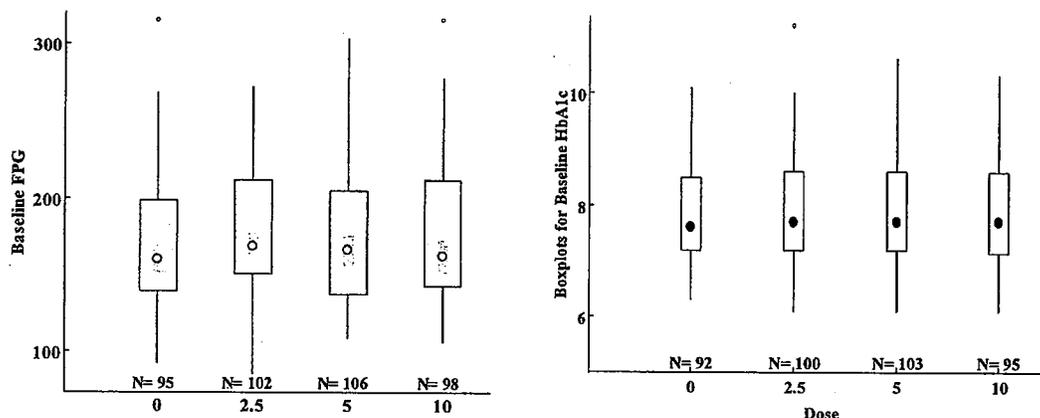
There were no notable differences among the treatment groups with regard to baseline demographics (Table 3.1.1.6). The average age of the study population was about 54 years and the majority was white. About half the patients were male and about half were recruited in sites within the USA. The median duration since diagnosis of Type 2 diabetes was a little more than 1 year and all but 10 patients had not taken anti-diabetic medication. About one-third of the patients reported a history of tobacco use. The most common presenting medical conditions were being overweight, hypercholesterolemia and hypertension.

Table 3.1.1.6 Study 11 Patient Demographics for All Randomized and Treated Patients

	Placebo n=95	SAXA 2.5 n=102	SAXA 5 n=106	SAXA 10 n=98
Age				
Mean (SD)	54 (12)	53 (10)	54 (12)	53 (11)
Range	23-75	25-77	18-77	23-75
%≥65years	19%	11%	19%	14%
Gender				
% female	51%	43%	49%	54%
Race				
White	83%	87%	88%	82%
Black	6%	5%	5%	6%
Amer. Ind.	4%	3%	3%	5%
Asian	3%	5%	4%	6%
Other	4%	0%	1%	1%
Country				
USA	56%	54%	52%	53%
Canada	21%	23%	25%	22%
Mexico	16%	17%	16%	17%
Australia	3%	3%	4%	3%
Taiwan	2%	2%	2%	3%
Puerto Rico	2%	2%	2%	1%
Baseline BMI				
Mean (SD)	32 (5)	33 (5)	32 (5)	32 (5)
% ≥ 30	56%	65%	62%	64%
Duration T2 Diab				
Median yrs	1.4	1.7	1.3	1.1
Hx of				
Being overwt.	57%	63%	68%	62%
Hyperchol.	47%	32%	55%	39%
Hypertension	48%	43%	49%	50%
Tobacco use	32%	31%	32%	29%

The treatment groups were also well-balanced on HbA1c and FPG as the boxplots on the following page illustrate (Figure 3.1.1.4). This balance is particularly important because rescue is highest for those with high HbA1c or high FPG at baseline; so an imbalance in these variables would predispose a group to a higher rate of rescue compared to other groups.

Figure 3.1.1.4 Boxplots of baseline FPG and baseline HbA1c by treatment group



Efficacy Results

The analytical model described in the protocol was an analysis of covariance (ANCOVA) model including terms for treatment and baseline. In addition, to analyzing the data using an ANCOVA model, the applicant, as a sensitivity analysis, performed a repeated measures analysis of the HbA1c data. Analyses of completers and of patients who adhered to the protocol were also conducted. The applicant also performed tests for interactions for several subgroups including baseline HbA1c and race. For the primary efficacy analysis, to adjust for multiple comparisons, the applicant used an alpha level of 0.019 for each comparison of each saxagliptin dose to placebo. For secondary endpoints, analyses were planned only for those comparisons which showed a statistically significant effect over placebo for the primary endpoint of HbA1c.

The primary analysis population was all randomized patients with at least one post-baseline HbA1c measure. An analysis of completers included all patients with efficacy data at week 24.

This reviewer is focusing here on the primary efficacy results, HbA1c change from baseline at Week 24. In addition to including baseline HbA1c in the ANCOVA model, this reviewer has included a term for USA/non-USA to account for the USA/non-USA difference in rescue shown in Figure 3.1.1.3 on page 11.

The results of the reviewer's analyses are shown in Table 3.1.1.7 on the following page. Each dose compared to placebo was statistically significant with respect to change from baseline at endpoint (Week 24 last observation carried forward [LOCF]) after adjustments for multiple comparisons. The treatment differences computed by this reviewer differ from the applicant's by about 0.01 with lower results from the reviewer's model including USA/non-USA as a term; this difference is not notable and did not result in any differences in conclusions regarding the efficacy of each dose. The largest improvement is seen for saxagliptin 10 mg; however, this improvement over the other doses is small and unlikely to be of clinical importance.

Table 3.1.1.7 Study 11 HbA1c efficacy results for ITT population

	Placebo n=92	SAXA 2.5 n=100	SAXA 5 n=103	SAXA 10 n=95
Baseline	7.9 (0.9)	7.9 (0.9)	8.0 (1.1)	7.8 (0.9)
Change from Baseline Mean (SD)				
Week 24 LOCF	+0.19 (1.2)	-0.43 (1.0)	-0.47 (1.0)	-0.53 (0.8)
Week 24 OC	-0.28 (0.8) (n=55)	-0.59 (1.1) (n=72)	-0.61 (0.8) (n=71)	-0.67 (0.7) (n=67)
Treatment differences from placebo	NA			
LS Mean (95% CI)				
Week 24 LOCF		-0.61 (-0.9, -0.3)	-0.62 (-0.9, -0.3)	-0.72 (-1.0, -0.4)
Week 24 OC		-0.19 (-0.5, +0.1)	-0.19 (-0.5, +0.1)	-0.28 (-0.6, -0.01)
% HbA1c < 7% at endpoint				
All pts	24%	35%	38%	41%
By baseline median				
< 7.7%	41%	55%	67%	67%
≥ 7.7%	5%	16%	13%	16%
% Rescued based on FPG				
All pts	27%	14%	20%	15%
By baseline median HbA1c				
< 7.7%	10%	2%	0%	4%
≥ 7.7%	47%	25%	38%	25%
Applicant's repeated measures analysis results				
LS mean difference from placebo (95% CI)		-0.51 (-0.8, -0.3)	-0.51 (-0.8, -0.3)	-0.60 (-0.9, -0.4)

Reviewer's ANCOVA model included USA/non-USA in the model with baseline HbA1c and treatment

A little more than a third of the saxagliptin patients compared to ¼ of the placebo patients achieved an HbA1c level of 7% or less at endpoint with the majority of these patients having a baseline HbA1c level below 7.7% (the baseline median). Only about 15% of the saxagliptin patients with baseline HbA1c of 7.7% or greater had an endpoint value of 7% or less (Table 3.1.1.5). A comparison of the saxagliptin 5 mg dose to placebo for percentage of patients with values of 7% or less at endpoint yielded an odds ratio of 1.9 (95% CI of 1.0 to 3.6, marginally significant at p=0.04).

For patients completing the short-term period, no dose was statistically significantly different from placebo. Also a large difference in treatment effects (-0.4) is seen between the ITT population of all randomized patients (LOCF analysis or repeated measures analysis) and the completers which would be expected given that patients who stay on trial generally will continue to improve. The applicant's repeated measures results are consistent with the Week 24 LOCF results. Figure 3.1.1.6 on the following page illustrates the mean HbA1c change from baseline by cohorts defined by the week of dropout; the last graph then is a plot of data from patients who completed the trial. These graphs illustrate superiority for saxagliptin over placebo across all the cohorts; this is supportive of the primary results based on LOCF imputation.

As mentioned earlier, there was a significant difference in rescue between the saxagliptin groups and placebo which as a measure of lack of efficacy is supportive of the efficacy of saxagliptin.

None of the results in Table 3.1.1.7 suggest a dose response with similar results for all three doses; this is further illustrated in the boxplot of the change from baseline in HbA1c at endpoint (Figure 3.1.1.5)

Figure 3.1.1.5 Boxplots of change from baseline HbA1c Week 24 LOCF by treatment group

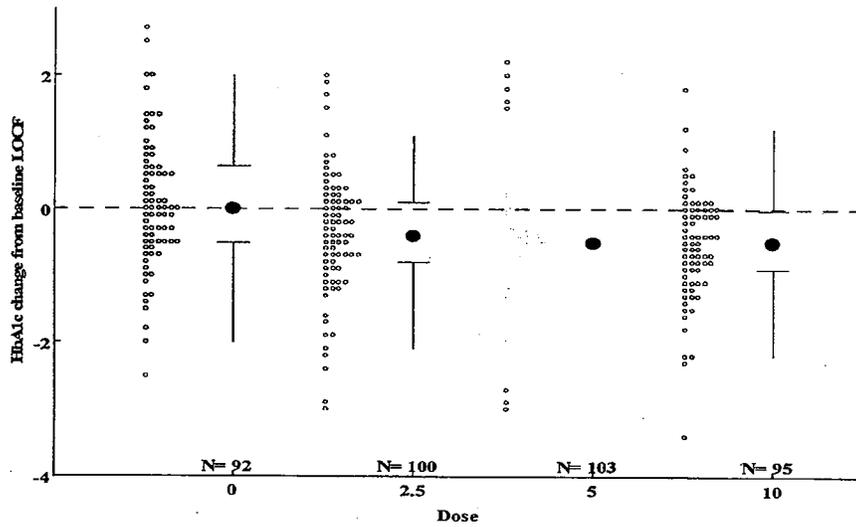
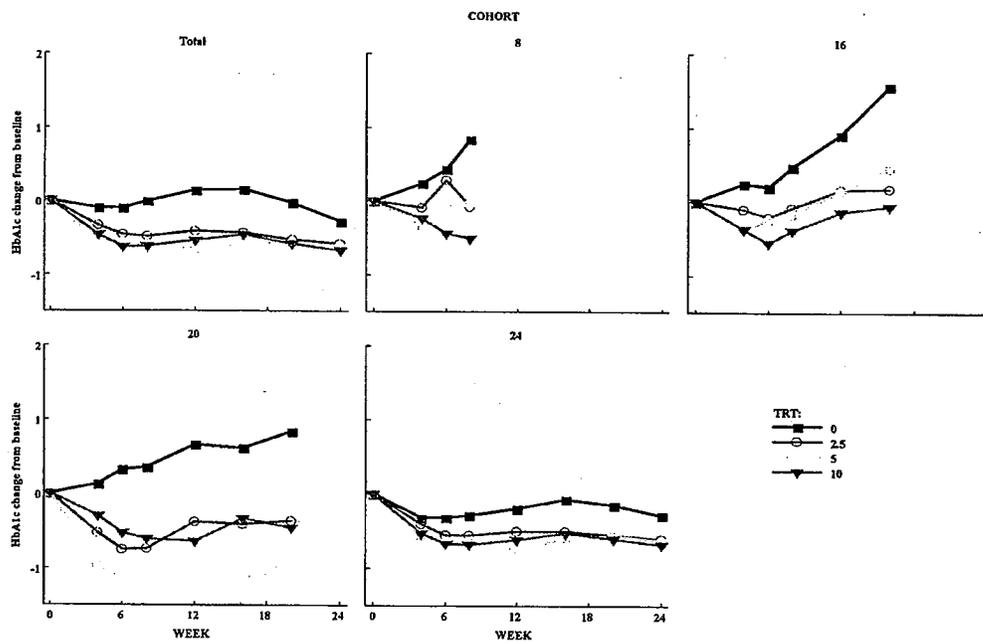


Figure 3.1.1.6 Means of change from baseline HbA1c over 24 weeks by cohorts defined by completion times



The applicant reports in the study report () that significant treatment differences are seen as early as Week 4 for HbA1c and Week 2 for FPG. No analyses by week were planned according to the protocol and so these analyses at Weeks 2 and 4 are post hoc and clearly would not have been mentioned had the results not been positive. From a statistical perspective, ()
() Also, it should be noted that the differences in HbA1c of ~0.4 at Week 4 may not be considered clinically relevant.

b(4)

Study 38

Design

Study 38 is a double-blind, randomized Phase 3 trial with 5 treatment arms; saxagliptin 2.5 mg once in the morning (QAM, referred to as 2.5AM in this review), saxagliptin 2.5 mg QAM with possible titration to 5 mg QAM (2.5tAM), saxagliptin 5 mg QAM (5AM), saxagliptin 5 mg taken prior to the evening meal (QPM, 5PM) or placebo (PLA). After screening, patients entered a 2-week placebo lead-in and then were randomized, if entry criteria were met. Randomized patients were followed for 24 weeks for efficacy.

Entry criteria included the following:

- $7\% \leq$ screening HbA1c $\leq 10\%$
- Naïve to anti-hyperglycemic therapy
- No symptoms of poorly controlled diabetes
- No significant cardiovascular history; no CHF Stage III or IV
- No active liver disease

Based on the criteria in Table 3.1.1.8, patients randomized to the 2.5 mg titratable arm could have the saxagliptin dose titrated as early as Week 4. Titration to 5 mg could also take place at Weeks 8, 12 and 24. Patients in all groups could be rescued with open-label metformin according to the criteria in Table 3.1.1.9; rescued patients were discontinued from the 24-week segment of the trial but remained on double-blind treatment during a long-term extension. Patients rescued are counted as dropouts due to lack of efficacy.

Table 3.1.1.8 Study 38 Titration criteria for patients randomized to the 2.5 mg QAM arm where titration was allowed (Table 3.1.2A in the applicant's study report)

Visit	Mean Fasting Plasma Glucose (MFG) ^a	Mean Fasting Whole Blood Glucose (MFWBG) ^a
Week 4	≥ 150 mg/dL (8.3 mmol/L)	≥ 140 mg/dL (7.7 mmol/L)
Week 8	≥ 140 mg/dL (7.7 mmol/L) and ≤ 220 mg/dL (12.2 mmol/L)	≥ 131 mg/dL (7.2 mmol/L) and ≤ 203 mg/dL (11.3 mmol/L)
Weeks 12 and 24	≥ 126 mg/dL (7.0 mmol/L) and ≤ 200 mg/dL (11.1 mmol/L)	≥ 118 mg/dL (6.5 mmol/L) and ≤ 185 mg/dL (10.3 mmol/L)

^a The calculation of mean fasting glucose (MFG) was based on fingerstick data from subject self blood glucose monitoring for at least 3 of the 5 days preceding the visit.

Table 3.1.1.9 Study 38 Rescue criteria (Table 3.1.2B in the applicant's study report)

Visit	Mean Fasting Plasma Glucose ^a	Mean Fasting Whole Blood Glucose ^a
Week 6	> 240 mg/dL (13.3 mmol/L)	> 221 mg/dL (12.3 mmol/L)
Week 8	> 220 mg/dL (12.2 mmol/L)	> 203 mg/dL (11.3 mmol/L)
Weeks 12, 16, 20 and 24	> 200 mg/dL (11.1 mmol/L)	> 185 mg/dL (10.3 mmol/L)

^a The calculation of mean fasting glucose was based on fingerstick data from subject self blood glucose monitoring for at least 3 of the 5 days preceding the visit. The primary outcome variable in this trial was HbA1c at Week 24 or endpoint (last-observation-carried-forward before rescue). The primary objective was to compare the four saxagliptin QAM arms to placebo. A comparison of the saxagliptin QPM arm to placebo was named as a secondary objective. The protocol contains no plans to compare the QAM dosing to the QPM dosing. The latter is clearly a relevant comparison for patients so this reviewer will compare the 5 mg QAM to the 5 mg QPM. Also the protocol fails to state the reason for the titration arm. No analyses comparing the titration arm to other saxagliptin arms were planned according to the protocol.

Patient disposition

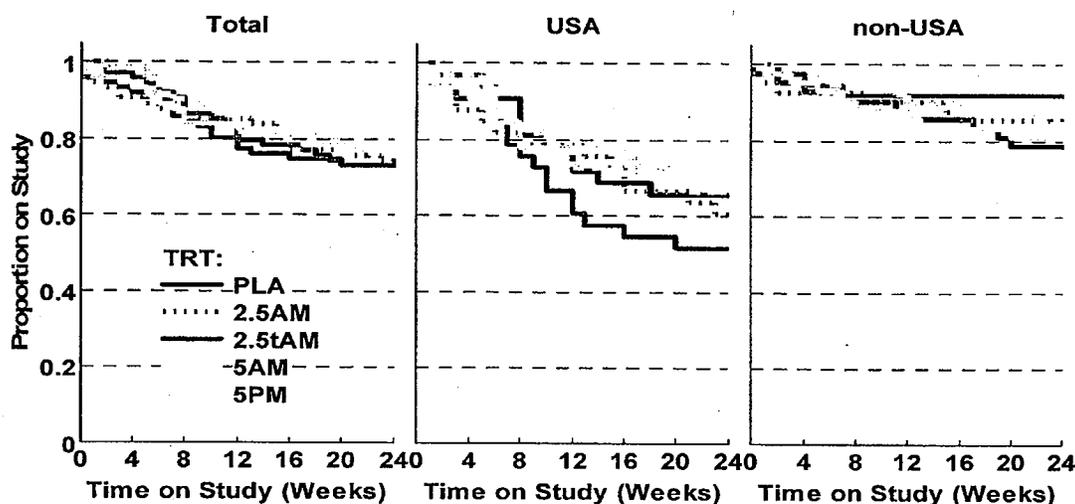
A total of 365 patients were enrolled at 72 sites in USA (49 sites), Russia, India and Taiwan with about 75% of the patients completing 24 weeks (Table 3.1.1.10). The primary reason for discontinuing from the short-term 24-week period was rescue for lack of glycemic control (for the criteria, see Appendix 6.1). The rescue rates are essentially the same across the groups though Figure 3.1.1.7 illustrates that the titration group has the highest rate of discontinuation in the US sites; also as was seen in other studies the highest discontinuation rates are seen for the USA, nearly double what is seen in non-USA sites.

Table 3.1.1.10 Study 38 Reasons for discontinuation during 24-week period for patients randomized and treated

	Placebo n=74	2.5AM n=74	2.5tAM n=71	5AM n=74	5PM n=72
Rescued	11 (15%)	8 (11%)	9 (13%)	10 (14%)	8 (11%)
ADE	1 (1%)	0	2 (3%)	0	1 (1%)
Pt request	4 (5%)	4 (5%)	1 (1%)	4 (5%)	5 (7%)
Lost-to-follow-up	3 (4%)	4 (5%)	2 (3%)	2 (3%)	3 (4%)
Other	1 (1%)	3 (4%)	4 (6%)	1 (1%)	0
Completed 24 weeks	53 (72%)	55 (74%)	52 (73%)	57 (77%)	55 (76%)

Numbers extracted from applicant's study report.

Figure 3.1.1.7 Study 38 Patient disposition for all sites and by USA/non-USA sites



Patient baseline demographics

There were no important differences in baseline demographics across the treatment groups (Table 3.1.1.11). The average age was 55 with about 17% 65 or older. Patients were for the most part newly diagnosed with diabetes (median about six months, mean about 2 years). Of all the Phase 3 trials, Study 38 had the highest rate of coronary artery disease (CAD) at 13% compared to about 5% in other studies. Only 5% of the patients had been previously treated with anti-diabetic drugs.

Table 3.1.1.11 Study 38 Patient Demographics for All Randomized and Treated Patients

	Placebo n=74	2.5AM n=74	2.5tAM n=71	5AM n=74	5PM n=72
Age					
Mean (SD)	56 (10)	55 (10)	54 (11)	55 (10)	55 (10)
%≥65years	18%	22%	17%	16%	15%
Gender					
% female	53%	66%	48%	49%	54%
Race					
White	72%	68%	76%	66%	67%
Asian	23%	24%	20%	27%	22%
Other	5%	8%	4%	7%	11%
Country					
USA	43%	45%	47%	43%	46%
Russia	37%	32%	34%	34%	33%
India	15%	16%	16%	18%	14%
Taiwan	5%	7%	4%	5%	7%
Duration T2 Diab					
Median yrs	0.4	0.5	0.6	0.6	0.4

Efficacy results

According to the protocol, four comparisons of each saxagliptin dose to placebo were performed in a sequential manner as follows:

Step 1: Compare SAXA 2.5AM to placebo and SAXA 5AM to placebo adjusting for multiple comparisons using Dunnett's test (alpha of 0.027)

Step 2: If one of the tests under Step 1 is statistically significant, then compare SAXA 2.5tAM vs. PLA at alpha of 0.027.

If both tests under Step 1 are statistically significant, then compare SAXA 2.5tAM vs. PLA at alpha of 0.05.

Using the sequential procedure described above for adjusting for multiple comparisons, all comparisons were statistically significant at $p < 0.02$ and thereby met the criteria for significance.

Table 3.1.1.12 Study 38 HbA1c Week 24 LOCF LS Means and Standard Errors for ITT population
Applicant's results extracted from Table 7.1 of study report and checked by reviewer

	Placebo n=68	2.5AM n=67	2.5tAM n=69	5AM n=69	5PM n=70
Baseline	7.8 (0.1)	8.0 (0.1)	8.0 (0.1)	7.9 (0.1)	7.9 (0.1)
Change from Baseline	-0.3 (0.1)	-0.7 (0.1)	-0.6 (0.1)	-0.7 (0.1)	-0.6 (0.1)
Treatment differences from placebo	NA	-0.45 (0.1)*	-0.37 (0.1)*	-0.40 (0.1)*	-0.35 (0.1)*

* $p < 0.02$

The treatment effects for this study are notably lower than the effects that were seen for Study 11; for example, the treatment effect observed for the 5 mg dose in Study 11 was -0.62 while the effect in this study is much less at -0.40. Some of this difference may be due to the difference in rescue rates between the two studies with twice as many patients rescued in the Study 11 than in this study. Furthermore, the observed cases treatment effect for the 5 mg dose in Study 11 was -0.19 compared to -0.30 in Study 38.

Perhaps the most valuable information to be gained from this study is the comparison of AM dosing to PM dosing for the 5 mg group. The estimates in the table above suggest the results for these two groups do not differ; to check this, an additional analysis comparing the two groups directly and computing a 95% confidence interval for the difference was performed by this reviewer. This analysis yielded a treatment difference of -0.05 (negative value favors the 5 mg AM dose) with a 95% confidence interval of -0.33 to +0.23. Usually for active control studies for anti-diabetic products a non-inferiority margin of about 0.4 is used although in recent trials with Januvia as an active comparator, a margin of 0.3 has been used. The lower bound of -0.33, in a trial clearly not designed nor powered for non-inferiority comparisons, suggests that the dosing schedule difference is not clinically important.

3.1.2 Add-on Trials

The applicant has conducted three add-on trials (Studies 13, 14 and 40) where saxagliptin is added to open-label oral anti-diabetic therapy (Table 3.1.2.1). Because these trials are of similar design, they are reviewed in this section together. All three trials had a single blind placebo-controlled lead-in period on open label (OL) anti-diabetic oral treatment followed by a 24 week efficacy period and long-term extensions as long as 182 weeks. Patients were randomized if following the lead-in, they were considered inadequately treated on open label medication and placebo.

Table 3.1.2.1 Randomized, double-blind add-on trials

Study (# of centers)	Special Design Features	Patient Population	Treatment Groups N	Duration of treatment
CV181013	OL TZD SAXA add-on	TZD failures	TZD+SAXA 2.5 195 TZD+SAXA 5 186 TZD+Placebo 184	2-week lead-in 24 weeks 12 months+ LT ongoing
CV181014	OL MET SAXA add-on	MET failures	MET+SAXA 2.5 192 MET+SAXA 5 191 MET+SAXA 10 181 MET+Placebo 179	2-week lead-in 24 weeks 12 months+ LT ongoing
CV181040	OL Glyburide SAXA add-on	SU failure	GLY7.5+SAXA 2.5 248 GLY10+SAXA 5 253 GLY10+Placebo 267	4-week lead-in 24 weeks 12 months+ LT ongoing

Rescue criteria for these three trials is similar and is described in Appendix 6.1.

Patient disposition

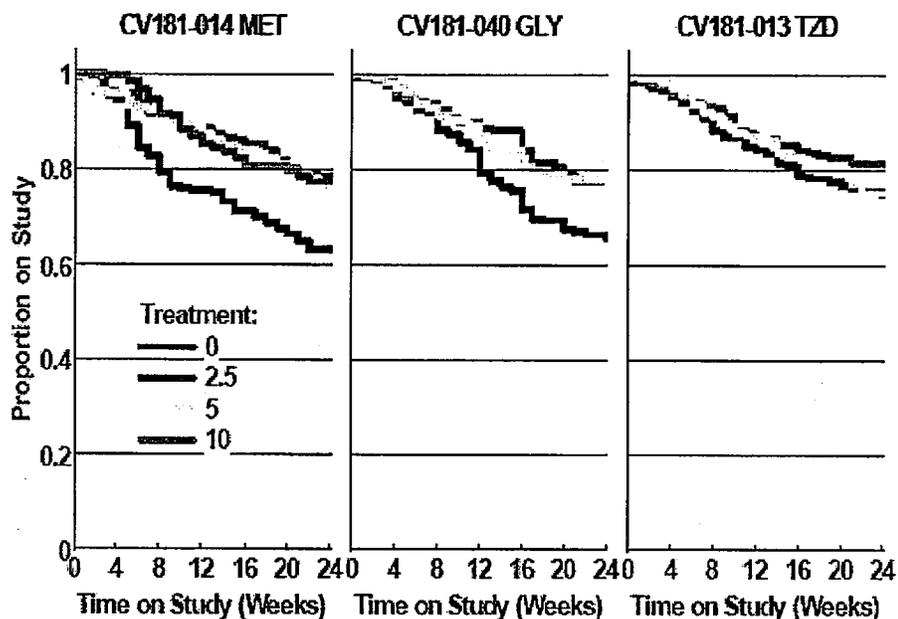
Individual sites at these three trials enrolled very few patients; Study 13 used 172 sites (117 US), Study 14 used 155 sites (92 US) and Study 40 used 132 sites (60 US). In Studies 13 and 14 about 190 patients were randomized in each group while in Study 40 about 60 more per group were randomized (Table 3.1.2.1).

Table 3.1.2.1 Patient disposition for add-on trials

	Placebo	SAXA 2.5	SAXA 5	SAXA 10
Randomized				
Study 13 TZD	184	195	186	NA
Study 14 MET	179	192	191	181
Study 40 GLY	267	248	253	NA
Rescued %				
Study 13 TZD	10%	9%	6.5%	NA
Study 14 MET	25%	13%	12%	15%
Study 40 GLY	25%	17%	15%	NA
ADE %				
Study 13 TZD	3%	1%	6%	NA
Study 14 MET	2%	3%	3%	3%
Study 40 GLY	1.5%	0.4%	2%	0.4%
Completers %				
Study 13 TZD	75%	81%	75%	NA
Study 14 MET	63%	77%	75%	77%
Study 40 GLY	66%	77%	77%	NA

The primary reason for discontinuing from the efficacy period was lack of glycemic control (Table 3.1.2.2). In Studies 14 and 40, about twice as many patients on placebo are rescued compared to the saxagliptin arms (Figure 3.1.2.1). The TZD add-on study is unusual compared to the other Phase 3 trials in that there is essentially no difference between the groups with regard to rescue. Completion rates for the 3 trials are about 77% in the saxagliptin groups. The discontinuation rate for USA studies is about 20% higher than the non-USA sites.

Figure 3.1.2.1 Patient Disposition (Time to discontinuation) for add-on trials



Baseline demographics

In the presentation of the demographic data for the three trials (Table 3.1.2.2), the treatment groups are pooled within study because there were no notable differences across the treatment groups and for ease of presentation. The patient population in the add-on trials is composed of patients that have all been previously treated with anti-diabetic medications; these patients then have an average of duration of diabetes about double what has been seen in the other studies in this application. With regard to other baseline parameters, these patients are similar to the patients seen in the monotherapy trials.

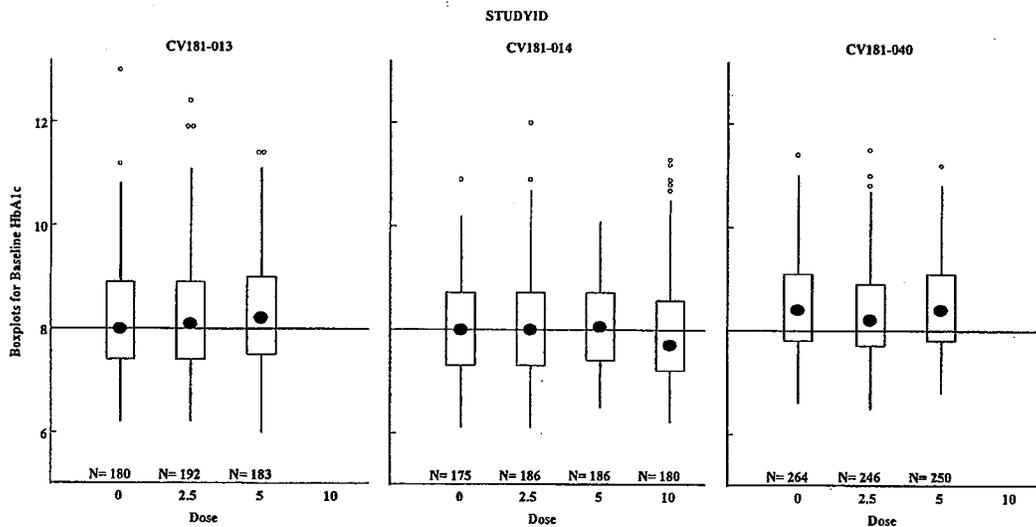
Table 3.1.2.2 Baseline demographics for the add-on studies with treatment arms combined

N	13 TZD	14 MET	40 GLY
	565	743	768
Age (years)			
Mean (SD)	54 (10)	55 (10)	55 (10)
Range	21-76	20-77	18-76
% ≥ 65 years old	15%	16%	18%
Gender			
% males	50%	51%	45%
BMI (kg/m ²)			
Mean (SD)	30 (6)	31 (5)	29 (5)
% ≥ 30	45%	57%	40%
Duration of Diabetes (yrs)			
Mean (SD)	5 (5)	6.5 (5)	6.9 (6)
History of CAD	4%	3%	3%
History of hypertension	55%	59%	53%
Previous diabetes treatment	100%	100%	100%
Used Baseline CV medication?	53%	58%	55%
HbA1c (%)			
Mean (SD)	8.3 (1.0)	8 (0.9)	8.4 (0.9)
% < 8%	45%	51%	33%
HDL-cholesterol (mg/dL)			
Mean (SD)	46 (10)	47 (10)	44 (11)
LDL-cholesterol (mg/dL)			
Mean (SD)	114 (36)	100 (32)	113 (34)

This is a partial reproduction of Table 5 created by this reviewer for the Advisory Committee Meeting briefing document.

Since treatment effect is related to baseline HbA1c, this reviewer is showing the distribution of baselines by trial and treatment group in Figure 3.1.2.1. There are no appreciable differences across groups within studies

Figure 3.1.2.1 Baseline HbA1c for add-on trials



Efficacy Results

The efficacy results summarized in Table 3.1.2.3 show statistically significant treatment differences for each dose compared to placebo in all three add-on trials regardless of analytical approach (LOCF or repeated measures). For the to-be-marketed dose of 5 mg, the treatment effects range from -0.6 to -0.8. The TZD add-on study showed the lowest decreases which is probably related to the lower rescue rates in this study for placebo compared to the other two studies (see 3.1.4 for more discussion of this issue).

Table 3.1.2.3 Add-on Studies HbA1c Efficacy Results Mean (SE)

	Placebo	SAXA 2.5	SAXA 5	SAXA 10
Baseline HbA1c				
Study 13 TZD	8.2 (0.1)	8.2 (0.1)	8.4 (0.1)	
Study 14 MET	8.1 (0.1)	8.1 (0.1)	8.1 (0.1)	8.0 (0.1)
Study 40 GLY	8.4 (0.1)	8.4 (0.1)	8.5 (0.1)	
Wk 24 LOCF				
Change from baseline				
Study 13 TZD	-0.3 (0.1)	-0.7 (0.1)	-0.9 (0.1)	
Study 14 MET	+0.1 (0.1)	-0.6 (0.1)	-0.7 (0.1)	-0.6 (0.1)
Study 40 GLY	+0.1 (0.1)	-0.5 (0.1)	-0.65 (0.1)	
Wk 24 LOCF				
LS Mean Trt Diff (95% CI)				
Study 13 TZD		-0.36 (-0.6, -0.2)*	-0.63 (-0.8, -0.4)*	
Study 14 MET		-0.73 (-0.9, -0.5)*	-0.83 (-1, -0.6)*	-0.72 (-0.9, -0.5)*
Study 40 GLY		-0.62 (-0.8, -0.5)*	-0.72 (-0.9, -0.6)*	
Repeated Measures Wk 24				
Trt Difference				
Study 13 TZD		-0.35 (-0.5, -0.2)*	-0.64 (-0.8, -0.5)*	
Study 14 MET		-0.73 (-0.9, -0.6)*	-0.82 (-1, -0.7)*	-0.69 (-0.9, -0.5)*
Study 40 GLY		-0.64 (-0.8, -0.5)*	-0.76 (-0.9, -0.6)*	

* p<0.001 Results were extracted from the applicant's report; LOCF results were checked by the reviewer. Studies 13 and 40 do not contain an arm with saxagliptin 10 mg so the SAXA 10 column is blank.

3.1.3 Trial of Saxagliptin plus Metformin as Initial Treatment

Study 39 (CV181-039) is a double-blind, randomized trial in naïve patients designed to study the efficacy and safety of saxagliptin administered with metformin with as initial treatment. Patients were randomized to one of four treatment arms; metformin monotherapy, saxagliptin monotherapy, metformin + saxagliptin 5mg or metformin + saxagliptin 10 mg.

The applicant describes this trial as active-controlled when in fact the trial is the standard combination trial design where the contribution of each component of the combination is assessed by comparing the combination to each component (i.e. placebo-controlled). The contribution of saxagliptin is measured by comparing the combination to metformin (saxagliptin+MET versus placebo+MET) and the contribution of metformin is measured by comparing the combination to saxagliptin (metformin+SAXA versus placebo+SAXA). One flaw in the design is that a 5 mg monotherapy arm of saxagliptin is not included so saxagliptin 10 mg must be used when assessing the combination of saxagliptin 5 mg and metformin.

The trial design was like all the other Phase 3 trials with a single-blind placebo lead-in (1 week instead of the 2 seen in other studies), a 24-week short-term efficacy assessment period of randomized double-blind treatment and a long-term period where double-blind treatment was continued on patients who completed the 24-week period or were rescued due to lack of glycemic control. The entry criterion for HbA1c for this trial differed from the other Phase 3 trials; Study 39 entered patients with baseline HbA1c of 8% to 12% while other studies used ~7% to 10% (Figure 1.3.1.1 on next page). The rescue criteria for this trial are described in Appendix 6.1.

Patient disposition

Study 39 is the largest Phase 3 trial in the saxagliptin database with a total of 1,306 patients randomized into 4 treatment groups at 196 sites (44 in USA and 46 in Russia) [Table 3.1.3.1]. Rescue was relatively low in the metformin and combination groups (6-8%) and about three times as high in the saxagliptin monotherapy group (20%). The highest completion rates were seen for the combination treatment (81%).

Table 3.1.3.1 Study 39 Reasons for discontinuation during 24-week period for patients randomized and treated

	MET	SAXA 5+MET	SAXA 10+MET	SAXA 10
Randomized	328	320	323	335
Rescued	27 (8%)	23 (7%)	18 (6%)	69 (20%)
LOE	3 (1%)	0	1 (<1%)	0
ADE	11 (3%)	7 (2%)	7 (2%)	8 (2%)
Pt request	13 (4%)	10 (3%)	17 (5%)	12 (4%)
Lost-to-follow-up	15 (5%)	11 (3%)	10 (3%)	15 (5%)
Other	16 (5%)	7 (2%)	9 (3%)	6 (2%)
Completed 24 weeks	243 (74%)	262 (82%)	261 (81%)	225 (67%)

Numbers extracted from applicant's study report.

The applicant's study report offers no discussion of the high rescue rate in the saxagliptin 10 mg groups so this reviewer examined the relationship between discontinuation for a few parameters that were shown to be related to rescue in Study 11 (baseline HbA1c, baseline FPG and BMI). First this reviewer noted that the distribution for the SAXA 10 group for baseline HbA1c is somewhat shifted upward compared to the other groups (see boxplots on the following page). A second graph on the following page illustrates the high dropout rate for the monotherapy group of saxagliptin 10 mg is seen in patients with high HbA1c at baseline (no difference was seen based on BMI). These results put into question the use of saxagliptin in

patients with very poor glycemic control.

Figure 3.1.3.1 Boxplots of baseline HbA1c by treatment group

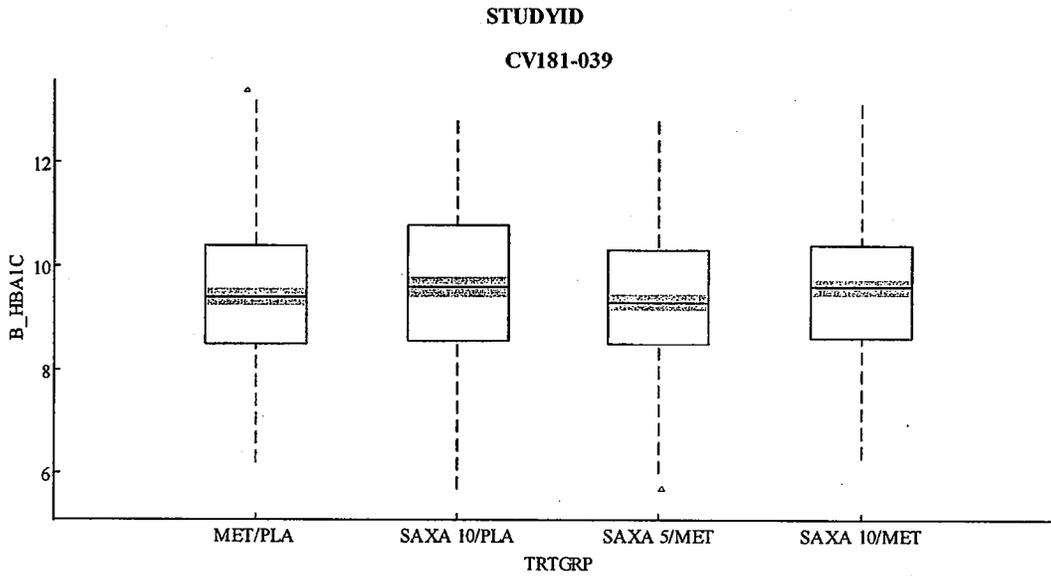
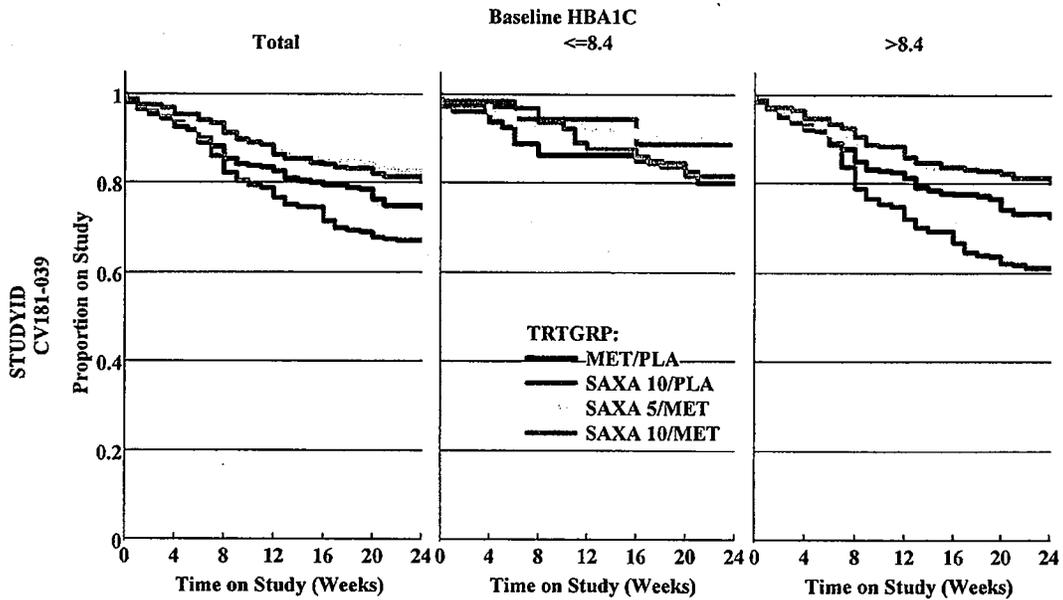


Figure 3.1.3.2 Patient disposition for all and by baseline HbA1c median



Baseline demographics

Study 39 enrolled patients naïve to anti-diabetic medication and newly diagnosed with Type 2 diabetes (median <1 year, mean ~ 2 years). This population was a little younger than patients in other Phase 3 trials (mean 52 years versus 55) with about 13% 65 or older. Of the 20+ countries enrolling patients, Russia enrolled the most (about 25%).

Table 3.1.3.2 Study 39 Patient Demographics for All Randomized and Treated Patients

	MET n=328	SAXA 5+MET n=320	SAXA 10+MET n=323	SAXA 10 n=335
Age				
Mean (SD)	51 (11)	52 (10)	52 (12)	52 (10)
%≥65years	11%	10%	17%	13%
Gender				
% female	50%	66%	48%	49%
Race				
White	77%	77%	75%	76%
Asian	16%	16%	17%	17%
Other	8%	7%	8%	7%
Country				
USA	11%	12%	12%	12%
Russia	26%	25%	26%	25%
India	10%	9%	10%	10%
Mexico	15%	15%	15%	15%
SA countries	14%	13%	13%	14%
Other (15 countries)	26%	26%	23%	25%
Duration T2 Diab				
Median yrs	0.4	0.4	0.3	0.4

Efficacy results

The primary endpoint was change from baseline in HbA1c at Week 24 with LOCF for imputing missing values. The LOCF means and the observed means for change range from -1.7 to -2.7 with the LOCF results not appreciably different from the OC results (Table 3.1.3.3). Treatment differences are summarized on the following page.

Table 3.1.3.3 Study 39 HbA1c Week 24 Mean (SD)

	MET n=313	SAXA 5+MET n=306	SAXA 10+MET n=315	SAXA 10 n=317
Baseline	9.4 (1.3)	9.4 (1.3)	9.5 (1.2)	9.6 (1.3)
Change from Baseline				
LOCF	-2.0 (1.5)	-2.5 (1.3)	-2.5 (1.3)	-1.7 (1.5)
OC	-2.3 (1.3)	-2.7 (1.2)	-2.7 (1.2)	-2.1 (1.5)

The numbers in this table were all computed by the reviewer.

Treatment effects are summarized in Table 3.1.3.4. (minus values favor saxagliptin). The p-values reported here are not adjusted because for a combination product, one must beat each component of the combination to declare the combination efficacious so a multiple comparison procedure is not needed.

To assess the effect of adding saxagliptin to metformin, the combination is compared to metformin alone; the results show an additional significant lowering of about 0.5 due to saxagliptin for both studied combinations. A larger effect is ascribed to the component of metformin with a lowering of about 0.8. Overall these results show that each component significantly contributes to the overall effect of the combination of saxagliptin and metformin.

Table 3.1.3.4 Week 24 LOCF Treatment differences LS Means (95% Confidence Intervals)

	LS Mean (95% CI)	p-value
SAXA 5+MET vs. MET	-0.53 (-0.7, -0.3)	<0.0001
SAXA 10+MET vs. MET	-0.50 (-0.7, -0.3)	<0.0001
SAXA 5+MET vs. SAXA 10	-0.84 (-1.0, -0.6)	<0.0001
SAXA 10+MET vs. SAXA 10	-0.80 (-1.0, -0.6)	<0.0001
SAXA 10 vs. MET	+0.30 (+0.2, +0.5)	<0.0001 favors MET

In addition, an analysis of saxagliptin 10 versus metformin was done by this reviewer and the difference seen there is the same as the difference seen for the metformin contribution (-0.8) and the saxagliptin contribution (0.5) with a treatment difference of 0.30 favoring metformin.

3.1.4 Impact of use of rescue medication on estimates of treatment effect

During the review of the efficacy of saxagliptin this reviewer observed that the treatment effect (Week 24 LOCF) of Study 38 was about 30% less than the effect seen in Study 11 and that one of the most obvious differences between these trials was the difference in rescue rates with a rate in Study 11 almost 3 times the rate seen in Study 38. To examine this relationship further, this reviewer is taking a rather simplistic approach and ordering the treatment effects by magnitude of rescue. This exercise is an attempt to illustrate the impact of rescue on the treatment effect estimates.

The magnitude of rescue can be characterized in a several ways; two ways chosen by this reviewer are: rescue in the placebo group (Figure 3.1.4.1) and overall rescue in the trial (Figure 3.1.4.2). The graphs below show the least square means treatment differences (saxagliptin 5 mg minus placebo) sorted by the two measures of rescue mentioned. These graphs suggest that increased rescue either within the placebo group or for both groups may result in larger estimates of effect. Furthermore these results may suggest that consideration should be given to other imputation schemes beyond LOCF. The LOCF approach has been shown by many to produce biased estimates and may not be appropriate for diabetes trials with large numbers of withdrawals due to lack of efficacy; further research is needed to examine this. Another issue that may play a role in the impact of rescue is the criteria used for rescue; for example, less stringent criteria may result in fewer dropouts and less impact. This issue then needs to be considered at the design stage.

Figure 3.1.4.1 LS Means Treatment Difference for SAXA 5 versus placebo sorted by the percentage of rescue in the placebo group (y-axis)

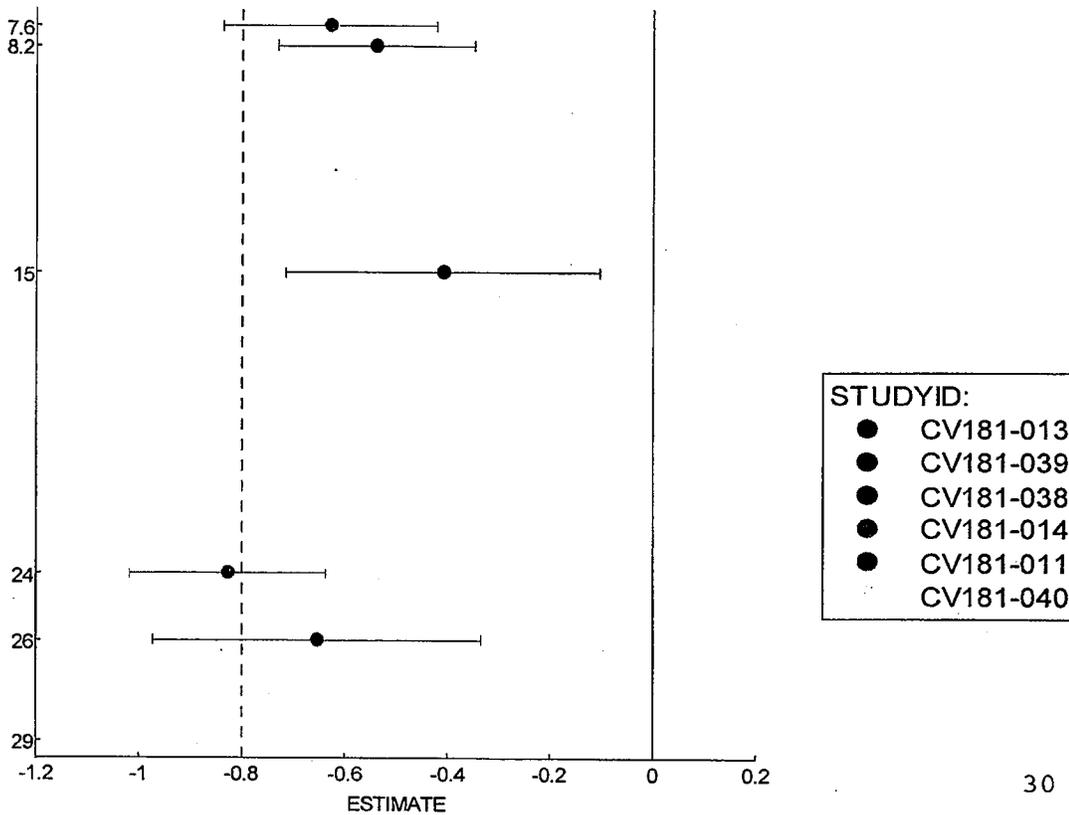
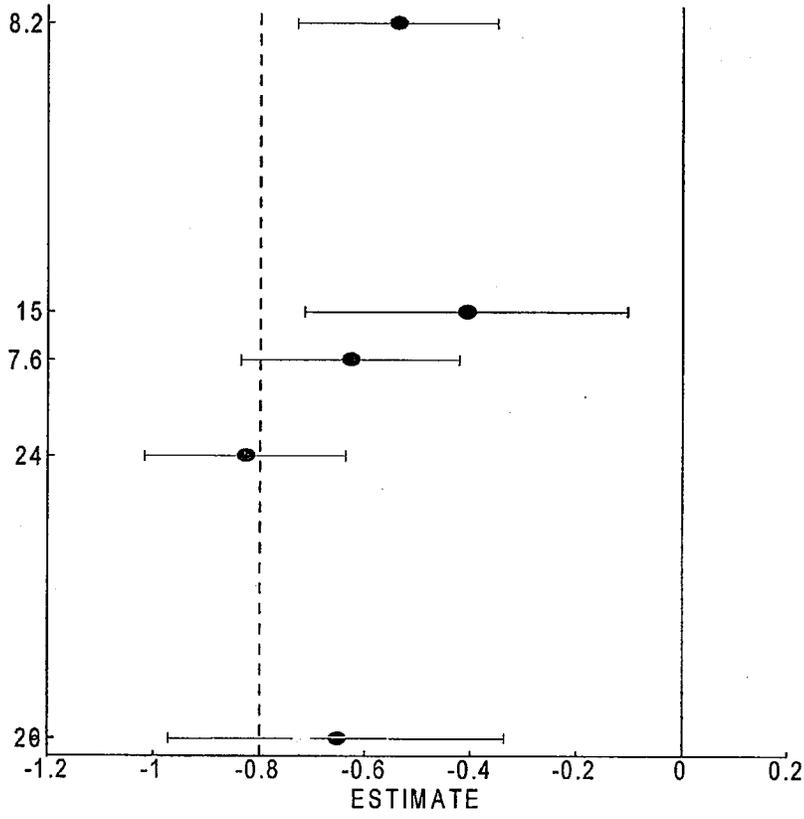


Figure 3.1.4.2 LS Means Treatment Difference for SAXA 5 versus placebo sorted by the percentage of rescue in the study overall (y-axis)



3.2 Evaluation of Safety

Potential safety issues included decrease in lymphocyte count and increased skin disorders. The lymphocyte changes are addressed in both the clinical pharmacology review and the FDA medical review. The medical reviewer has also thoroughly addressed the effect of saxagliptin on skin disorders in her review. Both of these safety issues appear to be minor and do not suggest the need for statistical input.

In December 2008, DMEP issued a guidance (“Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”) regarding the assessment of cardiovascular (CV) risk of new antidiabetic therapies. This guidance was issued after the saxagliptin application had been submitted to FDA, therefore all analyses to assess CV risk for saxagliptin were planned post hoc, after the data had been collected and summarized.

With regard to endpoints the guidance states, on page 6, the following:

Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

Because CV endpoints were not preplanned nor adjudicated in any of the saxagliptin studies, several definitions for major adverse cardiovascular events (MACE) were proposed by both the FDA and the applicant. These MACE endpoints are described in detail in the briefing documents for the April 1 Endocrine and Metabolic Drugs Advisory Committee Meeting.

The MACE results are summarized in the table below; for more details see the briefing documents for the advisory committee meeting. These results show that the Custom MACE results satisfy the 1.3 and 1.8 boundaries for the upper limit of the confidence intervals for the odds ratios set by the diabetes guidance for cardiovascular outcomes.

Table 3.2.1 Summary of MACE Results*

	Saxagliptin (n=3356)	Comparator (n=1251)	Common Odds Ratio Stratified on Study (95% CI)
Custom MACE			
ST	4 (0.1%)	7 (0.6%)	0.21 (0.04, 0.8)
ST+LT	23 (0.7%)	17 (1.3%)	0.52 (0.3, 1.0)
SMQ MACE			
ST	58 (1.8%)	25 (2.0%)	0.90 (0.6, 1.5)
ST+LT	100 (3.1%)	41 (3.2%)	0.96 (0.7, 1.4)

*The ST+LT database for the FDA analyses is the 120-day safety update database

The SMQ results were largely driven by events defined as “CPK increases.” This reviewer performed an analysis excluding these events which produced an estimate of 0.5 with a 95% confidence interval of 0.3 to 0.9, comparable to the Custom MACE results.

Because there was a higher incidence of CPK increases counted as adverse events for saxagliptin than placebo, this reviewer looked further at the CPK data based on recommendations from the clinical reviewer. Using the 120-Safety Update dataset for lab results, CPK values two times the upper limit of

normal that occurred at anytime during the short-term and long-term periods were identified. The results of the three trials with doses ranging from 2.5 mg to 10 mg are shown in Table 3.2.2. It is clear that there is no evidence of a treatment difference.

Table 3.2.2 Percentage of patients with at least one CPK value greater than 2xULN during the short and long term periods for three trials (Studies 11, 14 and 39)

	Placebo	Saxa 2.5	Saxa 5.0	Saxa 10
Study 11	13/93 14%	12/101 12%	11/105 11%	6/97 6%
Study 14	11/179 6%	9/189 5%	14/190 7%	20/181 11%

	Saxa 5 + Met	Saxa 10 + Met	Metformin	Saxa 10
Study 39	23/321 7%	26/322 8%	27/327 8%	31/334 9%

A member of the advisory committee of April 1 suggested that one additional analysis be performed in an attempt to identify a high risk population in a database that overall appears to be at low risk for a CV event. It was suggested that an analysis of patients with at least a 10 year history of diabetes for CV risk be performed.; the results (Table 3.2.3) show comparable odds ratios regardless of duration with an estimate of 0.3 for the subgroup of patients with at least 10 years duration of diabetes accompanied by a wide confidence interval. It should be noted that the placebo event rate for this subgroup is still quite low at 2% and therefore may not be indeed capturing a high risk population.

Table 3.2.3 Custom MACE results for short-term plus long-term data by subgroups defined by duration of diabetes

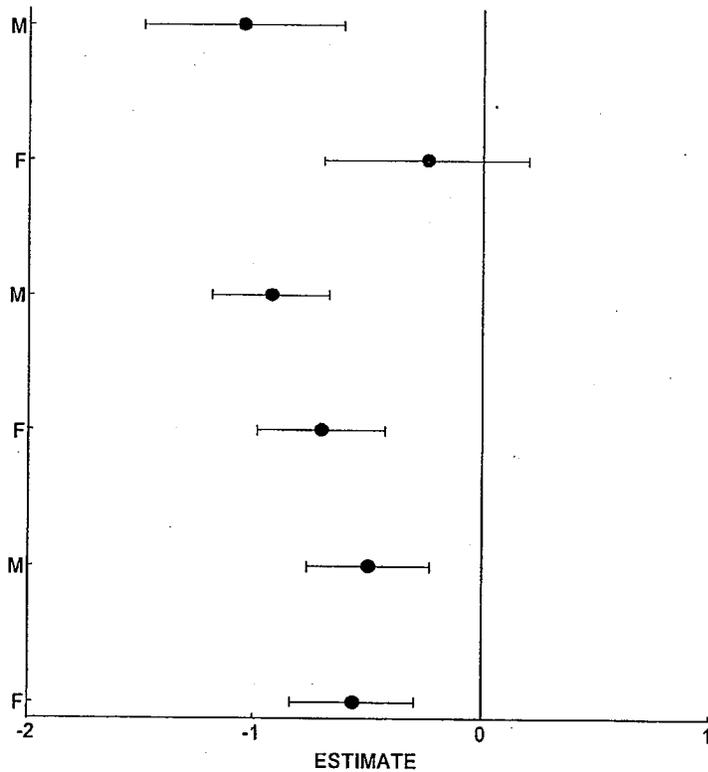
	Saxagliptin	Control	Stratified OR ¹ (95% CI)
Overall results	23/3356 (0.7%)	17/1289 (1.3%)	0.52 (0.3, 1.0)
Duration of diabetes			
<10 years	21/2661 (0.8%)	14/980 (1.4%)	0.55 (0.3, 1.2)
10 years +	2/339 (0.6%)	3/146 (2.1%)	0.30 (0.02, 3)

4. Findings in Special/Subgroup Populations

For the summary of subgroup results, only treatment effects for the proposed marketed dose of 5 mg of saxagliptin versus placebo using Study 11 (monotherapy), Study 14 (add-on to metformin) and Study 39 (initial combination treatment of metformin) are shown. The results are presented graphically and the results of interaction tests included in the accompanying text.

4.1 Gender, Race and Age

Figure 4.1.1 HbA1c treatment effect by gender

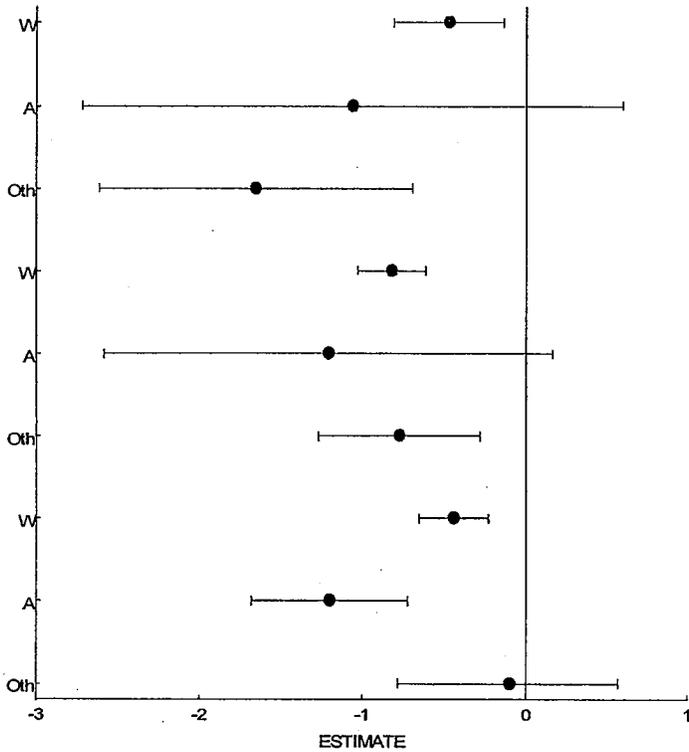


Only the analysis of Study 11 data yielded a statistically significant interaction for gender with a p-value of 0.01; a larger effect is seen for males than females. This subgroup difference was not observed in the other 2 studies depicted here.

There is no additional data that supports the subgroup difference seen for Study 11; for example the PK exposure data does not suggest a gender effect.

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● CV181-014
● CV181-039

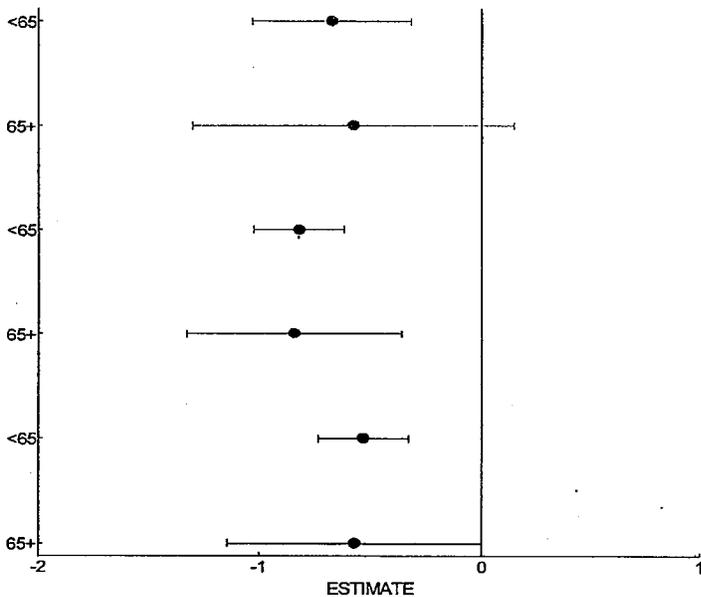
Figure 4.1.2 HbA1c treatment effect by race



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 • CV181-014
 • CV181-039

To assess race, this reviewer looked at a category for Caucasian (W on the graph), Asian (A on the graph) and all others (Oth on the graph). In all 3 studies the majority of the patients are Caucasian. Studies 11 and 14 each have only 7 Asians while Study 39 enrolled 95 Asians (about 15% of population). Two studies produced significant interactions; Study 11 with $p=0.07$ and Study 39 with $p=0.008$. The clinical implications of this finding for the treatment of Asians should be examined. This may raise questions regarding PK exposure and safety.

Figure 4.1.3 HbA1c treatment effect by age (<65 and 65+)

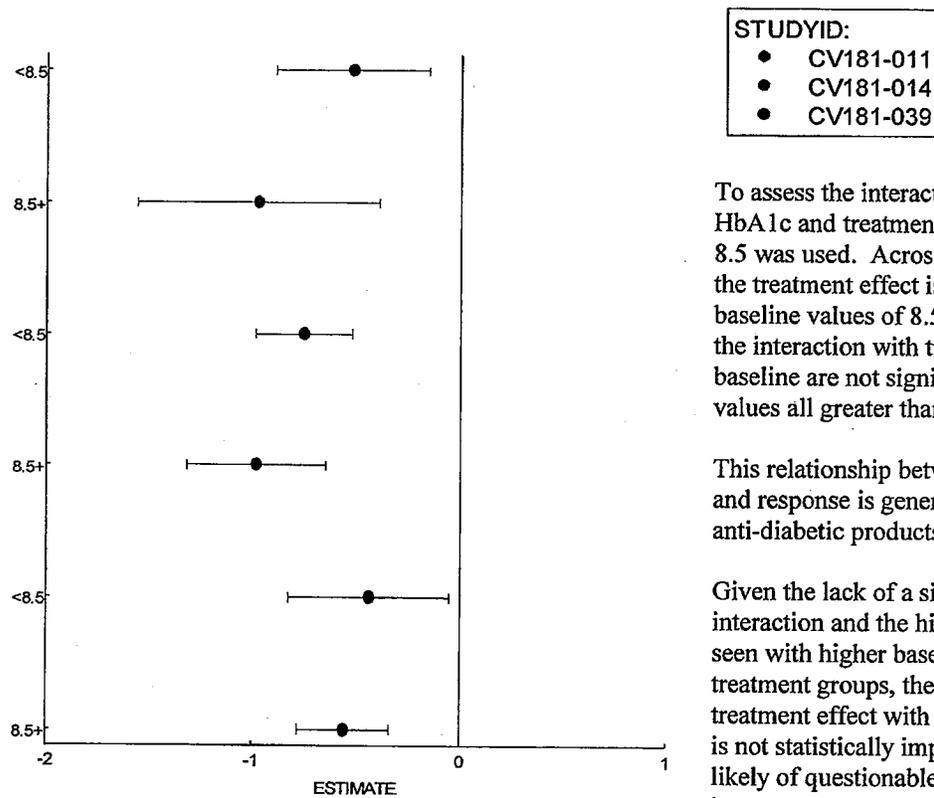


Consistent treatment effects were seen for patients under 65 and 65 and older for all three studies with interaction p-values all greater than 0.80.

4.2 Other Special/Subgroup Populations

The results of analyses based on subgroups defined by HbA1c at baseline, BMI, and USA/non-USA were planned by this reviewer. Recall that baseline HbA1c and BMI were both predictors of the use of rescue with higher values associated with more use of rescue. Also this reviewer found that higher rescue was associated with higher treatment effects (see Section). The results for BMI (cutpoint of 30) showed no significant interactions for any study ($p > 0.2$).

Figure 4.2.1 HbA1c Treatment effect by baseline HbA1c

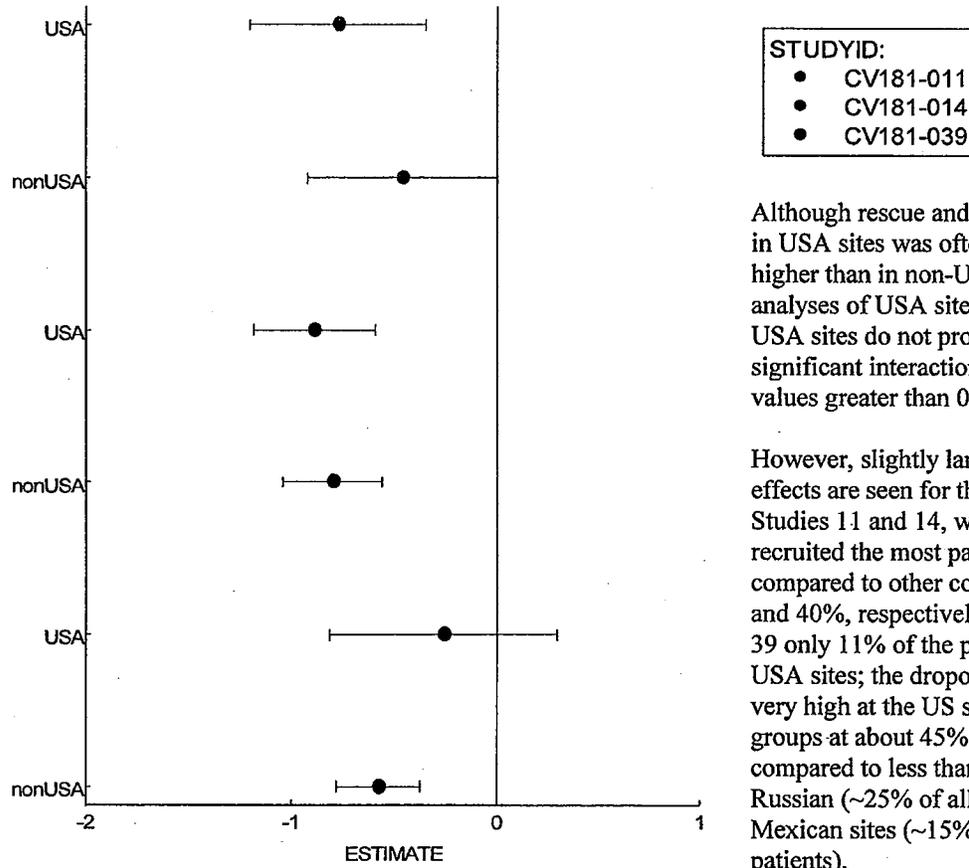


To assess the interaction of baseline HbA1c and treatment, a cutpoint of 8.5 was used. Across all three studies the treatment effect is larger for baseline values of 8.5 or greater but the interaction with treatment and baseline are not significant with p-values all greater than 0.20.

This relationship between baseline and response is generally seen for anti-diabetic products.

Given the lack of a significant interaction and the higher rescue rates seen with higher baselines in both treatment groups, the slightly higher treatment effect with higher baseline is not statistically important and most likely of questionable clinical importance.

Figure 4.2.2 HbA1c Treatment effect by USA/non-USA sites



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 • CV181-039

Although rescue and dropout rates in USA sites was often appreciably higher than in non-USA sites, analyses of USA sites and non-USA sites do not produce a significant interactions with all p-values greater than 0.29.

However, slightly larger treatment effects are seen for the USA in Studies 11 and 14, where the USA recruited the most patients compared to other countries (54% and 40%, respectively). For Study 39 only 11% of the patients were in USA sites; the dropout rate was very high at the US sites for all groups at about 45% overall compared to less than 20% at Russian (~25% of all patients) and Mexican sites (~15% of all patients).

These results are then consistent with the results seen in Section 3.1.4 of this review where we saw larger treatment effects associated with larger rescue rates.

5. Conclusions and Recommendations

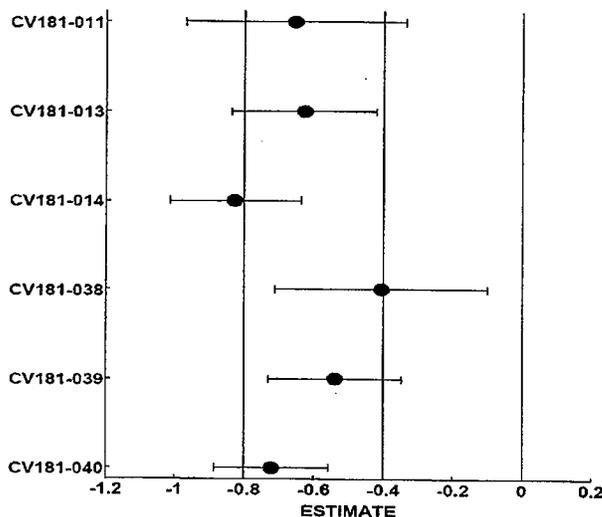
5.1 Summary and Conclusions¹

The applicant has submitted the results of eight clinical trials to support the efficacy and safety of saxagliptin for the treatment of Type 2 diabetes; six of these trials are Phase 3 clinical trials. These double-blind, randomized trials had several design features in common: a single-blind run-in period, a 24-week treatment period for assessing efficacy based on changes in HbA1c, an extension period of 12 or more months. The purpose of the extension period was to assess safety long-term. To enter this period, patients who were rescued with open-label therapy due to a lack of glycemic control were continued on double-blind treatment along with patients who completed the 24-week short-term period. For this review which primarily reports the efficacy findings, the focus is the data from the 24-week short-term period.

Two monotherapy studies provided data for assessing dose response; in Study 8, doses from 2.5 to 40 mg were compared to placebo while in Study 11, doses of 2.5, 5 and 10 were studied against placebo. Two other studies (Studies 14 and 39) included doses up to 10 mg in combination with metformin. No studies showed a dose response (see Figures 3.1.1.1 and 3.1.1.5); all studies showed statistically significant treatment effects for all doses of saxagliptin compared to placebo. One study (Study 39) contained both a metformin monotherapy arm and a saxagliptin 10 mg monotherapy arm; a comparison of these arms showed a decrease of 0.3 greater for metformin than saxagliptin. The applicant has chosen the dose of 5 mg for marketing with the 2.5 mg dose available for some special populations arguing that the 10 mg dose does not provide additional benefit and the 5 mg dose has a comparable safety profile to the 2.5 mg dose,

In addition to being studied as monotherapy, three trials examined the benefit of adding saxagliptin to an oral antidiabetic medication (TZD, metformin or glipizide) in patients inadequately treated on these medications. Another trial examined the efficacy and safety of saxagliptin and metformin in combination as initial therapy in patients naïve to antidiabetic treatment. In all four studies, statistically significant treatment effects were seen for all doses of saxagliptin studied.

Figure 1.1.1 HbA1c change from baseline Week 24 LOCF treatment difference for saxagliptin 5 mg versus placebo



The treatment differences for all 6 trials comparing saxagliptin 5 mg to placebo (Figure 1.1.1) show results favorable to saxagliptin ranging from -0.8 to -0.4; with five of the trials producing decreases of 0.5 or greater.

¹ This section is identical in content to the summary presented in Section 1.1 of this review.

High rates of rescue due to lack of glycemic control were generally associated with larger treatment differences for placebo versus saxagliptin (see Section 3.1.4). For most studies, rescue rates were higher for placebo patients than saxagliptin patients although this was not true in all studies and also there was no dose response regarding rescue. Notably higher rates of rescue were seen in USA sites than non-USA sites. In addition, the probability of rescue was increased with increased baseline HbA1c, FPG and BMI regardless of treatment. The implications of these findings for future trials should be examined. For example, the impact of stringent rescue criteria on rescue rates and, in turn, on the estimation of the treatment effect should be studied for differing designs which would help in the interpretation of future results. This reviewer believes the estimates computed for the saxagliptin trials are acceptable but that the difficulty arises when one interprets the estimates in the context of results for other products where trial designs may differ in ways that influence the magnitude of the effect.

In Study 39, a study of initial therapy with combination metformin and saxagliptin in naïve patients, the rescue rate in the monotherapy saxagliptin arm was notably high at 40%, about 20% higher than the rates seen in the other 3 treatment arms. This lack of efficacy is concerning given that Study 39 was a study of naïve patients with high baseline values (mean of about 9.5) and that saxagliptin was administered at the high dose of 10 mg. Considering also that, in general, high baseline HbA1c values are associated with high rescue (see Table 3.1.15), the efficacy of saxagliptin for these patients is clearly marginal.

Subgroup analyses based on gender, age, race, baseline HbA1c, and USA/non-USA revealed the following significant interactions:

- A larger treatment effect was seen for males than females in the large monotherapy study (Study 11, $p=0.01$) which was not replicated in other studies.
- Highly significant interaction ($p=0.008$) based on race in Study 39 showed Asians with the largest effect. This finding suggests that PK exposure should be studied and consideration given to assessing important safety findings in this subgroup.

This reviewer concludes that the applicant has adequately shown saxagliptin to be effective at lowering HbA1c based on six Phase 3 trials. Recommendations regarding the reporting of the efficacy in labeling are given in the next section.

3 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Appendix 6.1 Saxagliptin Phase 3 trials: Criteria for rescue and entrance in long-term extension

Study (# of centers)	% Completing 24 weeks		% Rescued in 24 week period		Criteria for rescue <i>Rescued pts continued into LT extension on DB trt</i>	Criteria for entering LT extension	Max Duration of Extension
	SAXA	Placebo	SAXA	Placebo			
CV181011 Monotherapy	69%	58%	16%	26%	Rescue with metformin OL Wk 4&6 FPG>240 Wk 8 FPG>220 Wk12-24 FPG>200	Completed ST or rescued during ST Continue DB treatment	18 months
CV181013 Add-on to TZD	78%	75%	8%	8%	Rescue with metformin OL Wk 4&6 FPG>240 Wk 8 FPG>220 Wk12-24 FPG>200	Completed ST or rescued during ST Continue DB treatment	12 months
CV181014 Add-on to MET	76%	63%	13%	25%	Rescue with pioglitazone OL Wk 4&6 FPG>240 Wk 8 FPG>220 Wk12-24 FPG>200	Completed ST or rescued during ST Continue DB treatment	42 months
CV181038 Monotherapy	75%	72%	12%	15%	Rescue with metformin OL Wk 6 FPG>240 Wk 8 FPG>220 Wk12-24 FPG>200	Completed ST or rescued during ST In DB LT: SAXA pts not rescued may titrate SAXA; placebo pts given fixed dose 500 mg blinded metformin	12 months
CV181039 SAXA+MET as initial therapy	SAXA+Met 81%	SAXA mono 67% Met mono 74%	6%	SAXA mono 31% Met mono 8%	Rescue with pioglitazone OL Wk 6 MFPG>240 Wk 8 MFPG>220 Wk12-24 MFPG>200 Mean FPG from finger stick	Completed ST or rescued during ST Continue DB treatment	12 months
CV181040 Add-on to GLY	77%	66%	17%	29%	Rescue with metformin OL Wk 4&6 MFPG>240 Wk 8 MFPG>220 Wk12-24 MFPG>200	Completed ST or rescued during ST Continue DB treatment and may titrate OL GLY	12 months

ST= initial short-term 24 week period LT= long-term extensions SAXA= saxagliptin treatment groups combined Placebo= placebo groups combined
Subjects can opt out at anytime; they are not specifically asked if they wish to continue into the extension but are continued if they fulfill the criteria. A check by this reviewer of a
few informed consent forms indicates that patients were expected to be committed to the ST plus LT at the onset of the trial. Patients were not asked whether they would like to
continue into the LT extension.

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/s/

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Thomas Permutt
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation
CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-350
Drug Name: BMS-477118 (Saxagliptin)
Indication(s): 104 Week Carcinogenicity in Rats and Mice
Applicant: Bristol Meyer and Squib Pharmaceuticals
717 Horikoshi, Fukuroi-shi, Shizuoka 437-0065, Japan
Test Facility: C >

b(4)

Documents Reviewed: Electronic submission, Dated: June 30, 2008
Electronic data submitted on Aug 28, 2008

Review Priority: Standard

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of BMS-477118 (Saxagliptin) in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Alavi.

2. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and two identical control groups. Three hundred and sixty Hsd:Sprague Dawley rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 25, 75, 150, and 300 mg/kg/day. Following the sponsor's definition, in this review these dose groups would be referred to as the low, mid-low, mid-high, and high dose group, respectively. The controls received the vehicle (reverse osmosis water) by gavage.

During the administration period each animal was observed twice daily for mortality, abnormalities, and signs of pain or distress. At least once prior to initiation, once weekly during dosing, and on the day of scheduled sacrifice, detailed observations were made on each animal for abnormal findings. In addition, palpation was performed once a week to detect grossly visible or palpable mass. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

Individual body weight data were collected at least once prior to treatment, weekly from Weeks 1 to 14, and once every 4 weeks thereafter (including Week 26) for all animals, during Week 96 for males and during Week 104 for males.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method. The dose response relationship¹ in mortality was tested using the two sided life table trend test. These tests used the pooled control groups, and were evaluated at the 0.05 level of significance. The two control groups, within each sex, were also tested for differences in survival.

Sponsor's findings: The sponsor reported that due to a drug-related decrease in survival, the 300 mg/kg/day male rats were terminated during Week 68 upon reaching 23% survival. Based on decreased survival in control males (<25%), the remaining groups of male rats were necropsied during Week 99. Final survivals in male rats were 22%, 15%, 35%, 27%, and 27% for the two controls, 25, 75, and 150 mg/kg/day groups, respectively. All female rats were necropsied after 104 weeks of dosing. Final survivals in female rats were 43%, 42%, 45%, 50%, 47%, and 50% for two controls, 25, 75, 150, and 300 mg/kg/day groups, respectively. Sponsor concluded that BMS-477118 did not affect the mortality rate of females in this study.

¹ In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

2.1.2. Tumor data analysis

The tumor data were analyzed using one-sided trend tests using methods suggested by Peto et al. (1980). Tumors observed only in an incidental context were analyzed by the prevalence method. Tumors observed only in a fatal context were analyzed by the death rate method. When a tumor was observed in both fatal and incidental contexts, the fatal and incidental occurrences were first analyzed separately and then the results were combined, as described in Peto et al. Mortality independent tumors, such as skin tumors, which were seen or palpated in one or more live animals, were analyzed by the onset rate method.

The asymptotic version of the Peto test was used whenever the total number of tumor bearing animals, summed across all dose groups, was greater than 12. When the total number of tumor bearing animals was 12 or less, the exact permutation method was used.

A Peto trend test was considered statistically significant if the one-sided P-value was less than 0.025 for a rare tumor, or less than 0.005 for a common tumor. A tumor that occurs with a background rate of 1% or less is considered to be rare; tumors with background rates higher than 1% are considered to be common (FDA Draft Guidance, 2001). If Peto test was showed a significant positive trend, a step-down analysis dropping the highest dose within the test was performed to find the highest dose level at which there was no statistically significant evidence of trend.

The analyses for the female rats were carried out as described above. The prevalence analyses used the National Toxicology Program (NTP) intervals discussed in the FDA Draft Guidance (2001).¹⁵ The NTP intervals are: 0-52 weeks, 53-78 weeks, 79-92 weeks, Week 93 to just before terminal sacrifice, and terminal sacrifice.

As stated above, the high dose males (300 mg/kg) were terminated at Week 68. Hence, the data from this group were not included in the Peto tests. The data from the other groups, which were terminated during Week 99, were subjected to Peto trend tests. These tests followed the same structure that was used for the female rats. This included using the NTP intervals for the prevalence analyses.

Sponsor's findings: Sponsor's analyses showed no statistically significant positive dose response relationship in any of the tested tumor types. The sponsor reported that pairwise comparison of 300 mg/kg/day group with the combined control for the increased incidence of astrocytoma in female rats approached a statistically significant increase; however, the observed incidence rate was within the historical background rate for aged female rats of this strain, at this laboratory.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. In this reviewer's analyses of both survival and tumor data, the two identical controls were combined to form a single control group. This combination reduces the dimension of the multiplicity of tumor data analysis and also increases the power of the tests. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

In this reviewer's analyses the survival of male rats were based on data from 0, 25, 75, and 150 mg/kg/day, while that of female rats were based on data from 0, 25, 75, 150, and 300 mg/kg/day. The survival

distributions of animals in all four treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: In male rats the tests showed no statistically significant dose response relationship or differences between the combined control and any of the treated groups in survivals across treatment groups in 0, 25, 75, and 150 mg/kg/day. Similarly, in female rats the tests showed no statistically significant dose response relationship or differences between the combined control and any of the treated groups in survivals across treatment groups in 0, 25, 75, 150, and 300 mg/kg/day.

2.2.2. Tumor data analysis

Since all animals from the 300 mg/kg/day dose group were sacrificed at week 68, in agreement with the reviewing pharmacologist, data from this dose group were not included in male rat primary tumor data analysis. However, an additional analysis for male rats was performed using all dose groups and the findings are given in Table 7A. For female rats the primary analysis was done using all dose groups. For comparison purpose with the male rats, an additional analysis for female rats was performed excluding the 300 mg/kg/day group and the findings are given in Table 7B. The tumor data were analyzed for dose response relationship and pairwise comparisons of combined control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998), which recommends to use a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two species, and a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the criteria developed by Haseman (1983), which recommends to use a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by the same authors (Rahman and Lin 2008) indicated similar usefulness of their recommendation for Poly-3 analysis also.

Reviewer's findings: Based on the criteria of adjustment for multiple testing for dose response relationship by Lin and Rahman, none of the tested tumor types showed a statistically significant positive dose response relationship in males or females, either using all dose groups or excluding the high dose group. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was

considered to be statistically significant in either sex for increased tumor incidence in the treated groups.

3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two identical control groups. Three hundred Crl:CD-1®(ICR)BR mice of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 50, 250, and 600 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The controls received the vehicle (reverse osmosis water) by gavage.

Each mouse was observed twice daily for mortality, abnormalities, and signs of pain or distress. At least once prior to initiation, once weekly, and on the day of scheduled necropsy, detailed observations were made on each mouse for abnormal findings. In addition, palpation was performed regularly to detect grossly visible or palpable mass. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

Individual body weight data were collected at least once prior to treatment, weekly for Weeks 1 to 14, once every 4 weeks thereafter (including Week 26), and at scheduled necropsy (all surviving animals).

3.1. Sponsor's analyses

3.1.1. Survival analysis

Survival data from the mouse study were analyzed using the same statistical methodologies as were used to analyze the survival data from the rat study.

Sponsor's findings: All male mice in 600 mg/kg/day group were sacrificed at week 90 when the survivor was reached 25%. At Week 100, when survival for males dosed with 250 mg/kg/day reached 25%, all remaining males from all groups were sacrificed. The sponsor's analysis showed that the final survivals in male mice were 51%, 38%, 36%, 25% and 25% in Control 1, Control 2, 50, 250, and 600 mg/kg/day groups, respectively. All females were sacrificed after 104 weeks of dosing. Final survival in females was 22%, 28%, 33%, 27%, and 27% in Control 1, Control 2, 50, 250, and 600 mg/kg/day groups, respectively.

Reviewer's comment: The reported survival rates on Page 14 of sponsor's submission in male Control 1, Control 2, and 50 mg/kg/day were 51%, 38%, and 36%, respectively. However, these rates were given as 51%, 36% and 38% in Control 1, Control 2, and 50 mg/kg/day in Table 2 in sponsor's submission. This reviewer's count showed a survival rate of 38% in 50 mg/kg/day group. It appears that the true survival in 50 mg/kg/day group is 38%. This discrepancy may be due to a typographical error on Page 14 of sponsor's submission.

There was a statistically significant dose-related increment in mortality in male mice. A trend test that included all dose groups was significant. In addition, a stepped down trend test that included only the controls, the 50 mg/kg group, and the 250 mg/kg/day group was also significant. The survival of the 50 mg/kg group was not significantly different from that of the controls. The lowest survival was in the 600 mg/kg group, and the survival of the 250 mg/kg/day group was below that of both the control groups and the 50 mg/kg/day group. There was no significant difference in survival between the two control groups. The test for dose related trends in mortality was not significant for the female mice. Survival in the two female control groups was comparable during the study.

3.1.2. Tumor data analysis

Tumor data from the mouse study were also analyzed using the same statistical methodologies as were used to analyze the tumor data from the rat study.

Sponsor's findings: Sponsor's analyses showed no drug related effects on the incidence of any neoplasm.

3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses from the mouse study. For the mouse data analyses this reviewer used similar methodologies as he used to analyze the data from the rat study. Also similar to analysis of rat data, for mouse survival and tumor data analysis this reviewer combined the two identical controls to form a single control group. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for males and females, respectively.

Reviewer's findings: Tests showed statistically significant dose response relationship in mortality in male mice. Also in male mice, pairwise comparisons showed statistically significant increased mortality in medium and high dose group compared to combined control.

3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pairwise comparisons of combined control and treated groups are given in Table 6A and 6B in the appendix for males and females, respectively.

Reviewer's findings: Based on the criteria of adjustment for multiple testing for dose response relationship by Lin and Rahman the incidence of none of the tested tumor types in either sex was considered to have a statistically significant positive dose response relationship. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the combined control was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of BMS-477118 (Saxagliptin) in rats and mice when administered orally by gavage at appropriate drug levels. Both of these studies were scheduled to conduct for about 104 weeks.

In this review, the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

Rat Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups and two identical control groups. Three hundred and sixty Hsd:Sprague Dawley rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 25, 75, 150, and 300 mg/kg/day. The controls received the vehicle (reverse osmosis water) by gavage. Tests showed no statistically significant dose response relationship or differences in survival across treatment groups in either sex. Tests did not show a statistically significant positive dose response relationship or increased incidence in treated group compared to the combined control in any of the tested tumor types.

Mouse Study: Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two identical one control groups. Three hundred Crl:CD-1@(ICR)BR mice of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The dose levels for treated groups were 50, 250, and 600 mg/kg/day. The controls received the vehicle (reverse osmosis water) by gavage. All animals in 600 mg/kg/day group were sacrificed at week 90 when the survivor was reached 25%. At Week 100, when survival for males dosed with 250 mg/kg/day reached 25%, all remaining males were sacrificed. All females were sacrificed after 104 weeks of dosing. Tests showed statistically significant dose response relationship in mortality in male mice. Also in male mice, pairwise comparisons showed statistically significant increased mortality in medium and high dose group compared to combined control. Tests did not show a statistically significant positive dose response relationship or increased incidence in treated group compared to the combined control in any of the tested tumor types.

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5. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	0 mg kg day		25 mg kg day		75 mg kg day		150 mg kg day	
	No. of Death	Cum. %						
0 - 52	5	4.17	2	3.33	3	5.00	5	8.33
53 - 78	36	34.17	7	15.00	16	31.67	13	30.00
79 - 91	39	66.67	19	46.67	17	60.00	16	56.67
92 - 98	16	80.00	11	65.00	8	73.33	10	73.33
Ter. Sac.	24	20.00	21	35.00	16	26.67	16	26.67
Total	N=120		N=60		N=60		N=60	

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Week	0 mg kg day		25 mg kg day		75 mg kg day		150 mg kg day		300 mg kg day	
	No. of Death	Cum. %								
0 - 52	5	4.17	3	5.00	2	3.33	5	8.33	6	10.00
53 - 78	19	20.00	10	21.67	11	21.67	14	31.67	11	28.33
79 - 91	24	40.00	10	38.33	6	31.67	5	40.00	7	40.00
92 - 104	21	57.50	10	55.00	11	50.00	8	53.33	6	50.00
Ter. Sac.	51	42.50	27	45.00	30	50.00	28	46.67	30	50.00
Total	N=120		N=60		N=60		N=60		N=60	

**Table 2A: Intercurrent Mortality Comparison
Male Rats
(Using data from 0, 25, 75, and 150 mg/kg/day)**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.6606
Homogeneity	Log-Rank	0.0682

**Table 2B: Intercurrent Mortality Comparison
Female Rats
(Using data from 0, 25, 75, 150, and 300 mg/kg/day)**

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.7472
Homogeneity	Log-Rank	0.8745

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats**

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	P_Value				
		Cont N=120	Low N=60	Mid-Low N=60	Mid-High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	
fff										
Adrenal, Cortex	B-Adenoma	11	3	3	3	0.8304	0.8277	0.7541	0.7681	
	M-Carcinoma	1	1	0	0	0.6845	0.6100	0.3419	0.3419	
Adrenal, Medull	B-Pheochromocytoma	23	15	7	6	0.9777	0.4519	0.8680	0.9258	
Body, Whole/Cav	M-Hemangiosarcoma	1	0	1	1	0.2770	0.3689	0.5761	0.5688	
	M-Histiocytic Sarcom	0	1	0	2	0.0569	0.3770	.	0.1169	
	M-Lrg Granular Cell	1	0	0	0	0.6188	0.3689	0.3419	0.3419	
	M-Lymphosarcoma	5	1	0	0	0.9873	0.7303	0.8821	0.8821	
Brain	B-Granular Cell Tumo	0	0	1	1	0.1184	.	0.3448	0.3448	
	M-Malignant Astrocyt	1	1	0	0	0.6845	0.6100	0.3419	0.3419	
	M-Malignant Oligoden	1	0	0	0	0.6219	0.3719	0.3448	0.3448	
	M-Meningeal Sarcoma	2	0	0	0	0.8559	0.6036	0.5688	0.5688	
Cavity, Abdomin	B-Lipoma	0	0	1	0	0.3980	.	0.3448	.	
Eye	M-Fibrosarcoma	1	0	0	0	0.6188	0.3689	0.3419	0.3419	
GI, Zymbal's	M-Carcinoma	2	0	0	1	0.4329	0.6036	0.5688	0.2689	
Jejunum	M-Carcinoma	0	0	1	0	0.3980	.	0.3448	.	
	M-Fibrosarcoma	0	0	0	1	0.1990	.	.	0.3448	
Kidney	M-Malignant Renal Me	0	1	0	0	0.3960	0.3770	.	.	
	M-Nephroblastoma	0	0	0	1	0.2030	.	.	0.3504	
Liver	B-Adenoma, Hepatocel	2	1	0	1	0.4984	0.3063	0.5688	0.2689	
Pancreas	B-Adenoma, Acinar Ce	1	0	1	1	0.2776	0.3719	0.5727	0.5727	
	B-Adenoma, Islet Cel	4	0	2	0	0.8438	0.8459	0.3340	0.8175	
	M-Carcinoma, Islet C	0	1	0	0	0.3960	0.3770	.	.	

(Continued)

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Rats**

(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	P_Value			
		Cont N=120	Low N=60	Mid-Low N=60	Mid-High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH
Parathyroid	B-Adenoma	0	0	0	1	0.1990	.	.	0.3448
Pituitary	B-Adenoma	14	10	6	4	0.8879	0.3816	0.5493	0.7894
Skin	B-Fibroma	1	0	1	1	0.2776	0.3719	0.5727	0.5727
	B-Keratoacanthoma	4	0	0	2	0.5124	0.8429	0.8141	0.3281
	M-Fibrosarcoma	2	0	1	0	0.7009	0.6074	0.2806	0.5727
	M-Malignant Basal Ce	0	0	1	0	0.3980	.	0.3448	.
	M-Sarcoma	0	1	0	0	0.3960	0.3770	.	.
Skin/Subq, Othe	B-Keratoacanthoma	7	0	0	1	0.9414	0.9615	0.9483	0.8189
	B-Papilloma, Squamou	1	1	2	0	0.5010	0.6139	0.2729	0.3448
	M-Carcinoma, Basal C	0	1	0	0	0.3980	0.3719	.	.
	M-Fibrosarcoma	2	0	0	0	0.8559	0.6036	0.5688	0.5688
Stomach, Nongl	M-Carcinoma, Squamou	0	1	0	0	0.3980	0.3719	.	.
Tail	B-Keratoacanthoma	2	2	3	1	0.4490	0.4803	0.2185	0.2689
Testis	B-Interstitial Cell	1	0	0	2	0.1250	0.3719	0.3448	0.2729
Thyroid	B-Adenoma, C-cell	13	17	11	11	0.2023	0.0138	0.1347	0.1347
	M-Carcinoma, C-cell	1	1	0	0	0.6881	0.6074	0.3448	0.3448
Urinary Bladder	M-Carcinoma, Transit	0	1	0	0	0.3980	0.3719	.	.

**3B: Dose Response Relationship Test and Pairwise Comparisons Using All Dose Groups
Female Rat**

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	300 mg	P_Value	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	P_Value C vs. H
		Cont N=120	Low N=60	Mid-Low N=60	Mid-Hi N=60	High N=60	Dos Resp				
Adrenal, Cortex	B-Adenoma	9	5	6	6	6	0.2615	0.5202	0.4200	0.3508	0.3683
	M-Carcinoma	0	0	2	1	1	0.1725	.	0.1163	0.3228	0.3281
Adrenal, Medull	B-Pheochromocytoma	3	2	1	4	1	0.4675	0.5417	0.4257	0.1512	0.4074
	M-Malignant Pheochro	0	0	1	0	1	0.1360	.	0.3435	.	0.3281
Body, Whole/Cav	B-Hemangioma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
	M-Hemangiosarcoma	0	1	0	0	1	0.1946	0.3333	.	.	0.3333
	M-Histiocytic Sarcom	0	0	1	0	0	0.3230	.	0.3435	.	.
	M-Lrg Granular Cell	2	0	0	0	0	0.8889	0.5573	0.5708	0.5432	0.5503
	M-Lymphosarcoma	2	0	0	1	0	0.6581	0.5573	0.5708	0.6930	0.5503
	M-Malignant Mesothe	0	0	0	1	0	0.3256	.	.	0.3281	.
Brain	M-Malignant Astrocyt	0	0	0	0	2	0.0272	.	.	.	0.1094
Cavity, Abdomin	B-Lipoma	0	0	0	1	0	0.3230	.	.	0.3228	.
Cervix	B-Polyp, Endometrial	3	1	2	1	2	0.3585	0.4166	0.5619	0.3885	0.5312
	M-Carcinoma	1	1	0	0	0	0.7765	0.5573	0.3435	0.3228	0.3281
Duodenum	B-Fibroma	0	0	0	1	0	0.3230	.	.	0.3228	.
	M-Sarcoma	0	0	0	1	0	0.3230	.	.	0.3228	.
Eye	M-Fibrosarcoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Gl, Zymbal's	B-Adenoma	0	0	0	0	1	0.1634	.	.	.	0.3281
Heart	M-Endocardial Schwan	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Kidney	B-Adenoma, Tubule Ce	0	0	0	0	1	0.1634	.	.	.	0.3281
	M-Fibrosarcoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281

(Continued)

**3B: Dose Response Relationship Test and Pairwise Comparisons Using All Dose Groups
Female Rat**

(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	300 mg	P_Value				
		Cont N=120	Low N=60	Mid-Low N=60	Mid-Hi N=60	High N=60	Dos Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	P_Value C vs.H
Liver	B-Adenoma, Hepatoce1	6	1	1	0	1	0.9040	0.7440	0.7623	0.9090	0.7343
Mammary, Female	B-Adenoma	2	0	0	1	0	0.6581	0.5573	0.5708	0.6930	0.5503
	B-Fibroadenoma	60	23	20	13	8	1.0000	0.9266	0.9789	0.9995	1.0000
	M-Carcinoma	15	2	0	3	1	0.9932	0.9620	0.9985	0.8809	0.9864
	M-Fibrosarcoma	0	0	1	0	0	0.3230	.	0.3435	.	.
	M-Sarcoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
	M-Schwannoma	0	0	1	0	0	0.3230	.	0.3435	.	.
Muscle, Other	M-Schwannoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Nerve, Other	M-Malignant Schwanno	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Ovary	B-Leiomyoma	0	0	0	0	1	0.1634	.	.	.	0.3281
	B-Luteoma	0	1	0	0	0	0.4981	0.3333	.	.	.
	M-Malignant Granulos	0	0	2	0	1	0.2085	.	0.1163	.	0.3281
Pancreas	B-Adenoma, Islet Cel	5	1	1	3	0	0.8462	0.6541	0.6740	0.5084	0.8684
	M-Carcinoma, Islet C	0	1	0	0	0	0.4981	0.3333	.	.	.
Pituitary	B-Adenoma	67	27	21	17	8	1.0000	0.8786	0.9902	0.9989	1.0000
	M-Carcinoma	0	1	1	1	0	0.4852	0.3333	0.3435	0.3228	.
Skin	B-Fibroma	1	0	1	0	0	0.6314	0.3333	0.5708	0.3228	0.3281
	M-Fibrosarcoma	0	1	0	0	0	0.4961	0.3385	.	.	.
	M-Leiomyosarcoma	0	0	1	0	0	0.3230	.	0.3435	.	.
skin/subq, othe	B-Basal Cell Tumor	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
	B-Keratoacanthoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
	B-Papilloma, Squamou	0	0	1	0	0	0.3230	.	0.3435	.	.
	M-Carcinoma, Basal C	0	1	0	0	0	0.4981	0.3333	.	.	.
	M-Fibrosarcoma	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281

(Continued)

**3B: Dose Response Relationship Test and Pairwise Comparisons Using All Dose Groups
Female Rat**
(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	300 mg	P_Value	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	P_Value C vs. H
		Cont N=120	Low N=60	Mid-Low N=60	Mid-Hi N=60	High N=60	Dos Resp				
Stomach, Nongl	M-Carcinoma, Squamou	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Tail	M-Leiomyosarcoma	0	0	1	0	0	0.3230	.	0.3435	.	.
Thymus	B-Adenoma	0	0	0	1	0	0.3230	.	.	0.3228	.
Thyroid	B-Adenoma, C-cell	28	22	11	10	13	0.8205	0.0344	0.7492	0.7665	0.4574
	M-Carcinoma, C-cell	0	1	2	1	0	0.5009	0.3333	0.1163	0.3228	.
Uterus	B-Polyp, Endometrial	39	11	13	11	8	0.9934	0.9673	0.9311	0.9423	0.9943
	M-Carcinoma	2	0	2	1	3	0.0699	0.5573	0.4257	0.6930	0.1982
	M-Carcinoma, Squamou	1	0	0	3	0	0.3595	0.3333	0.3435	0.1030	0.3281
	M-Leiomyosarcoma	0	0	0	0	1	0.1667	.	.	.	0.3333
	M-Sarcoma, Endometri	1	0	0	0	0	0.6654	0.3333	0.3435	0.3228	0.3281
Vagina	B-Polyp, Endometrial	0	0	0	1	1	0.0785	.	.	0.3228	0.3281

Table 4A: Intercurrent Mortality Rate in Male Mice

Week	0 mg/kg/day		50 mg/kg/day		250 mg/kg/day		600 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	15	12.50	6	10.00	16	26.67	17	28.33
53 - 78	18	27.50	10	26.67	9	41.67	14	51.67
79 - 91	20	44.17	9	41.67	10	58.33	14	75.00
92 - 99	17	58.33	12	61.67	10	75.00	.	.
Ter. Sac.	50	41.67	23	38.33	15	25.00	15*	25.00
Total	N=120		N=60		N=60		N=60	

*Terminal sacrifice of 600 mg/kg/day group took place on Week 91

Table 4B: Intercurrent Mortality Rate Female Mice

Week	0 mg/kg/day		50 mg/kg/day		250 mg/kg/day		600 mg/kg/day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	14	11.67	2	3.33	3	5.00	5	8.33
53 - 78	22	30.00	11	21.67	13	26.67	18	38.33
79 - 91	26	51.67	10	38.33	11	45.00	8	51.67
92 - 104	29	75.83	17	66.67	17	73.33	13	73.33
Ter. Sac.	29	24.17	20	33.33	16	26.67	16	26.67
Total	N=120		N=60		N=60		N=60	

Table 5A: Intercurrent Mortality Comparison Male Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	<.0001
Homogeneity	Log-Rank	0.0001

Table 5B: Intercurrent Mortality Comparison Female Mice

Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.8279
Homogeneity	Log-Rank	0.4986

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons Male Mice

Organ Name	Tumor Name	0 mg	50 mg	250 mg	600 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=60	High N=60	Dos Resp			
ADRENAL, CORTEX	B-ADENOMA, SUBCAPSUL	0	1	1	0	0.3226	0.3413	0.2966	.
ADRENAL, MEDULL	B-PHEOCHROMOCYTOMA	0	1	0	0	0.3443	0.3360	.	.
BRAIN	B-HEMANGIOMA	0	0	1	0	0.3443	.	0.2966	.
EPIDIDYMISS	M-FIBROSARCOMA	1	0	0	0	0.5634	0.3333	0.2941	0.2619
GALLBLADDER	B-PAPILLOMA	0	0	1	0	0.3443	.	0.2966	.
HARDERIAN GLAND	B-ADENOMA	10	6	1	4	0.5858	0.4625	0.8873	0.5470
	M-CARCINOMA	0	0	0	1	0.1596	.	.	0.2698
HEMATO NEOPLASI	M-LYMPHOMA	7	2	1	1	0.8368	0.6422	0.7320	0.6787
	M-SARCOMA, HISTIOCYT	3	0	1	0	0.7566	0.7073	0.3370	0.6048
KIDNEY	B-ADENOMA, TUBULAR C	1	0	0	0	0.5660	0.3360	0.2966	0.2640
	M-CARCINOMA, TUBULAR	1	0	0	0	0.5660	0.3333	0.2941	0.2640
	M-HEMANGIOSARCOMA	1	0	0	0	0.5660	0.3360	0.2966	0.2640
LIVER	B-ADENOMA, HEPATOCEL	7	1	2	1	0.7512	0.8264	0.5325	0.6751
	B-HEMANGIOMA	0	1	1	1	0.1240	0.3360	0.2966	0.2698
	M-CARCINOMA, HEPATOC	10	1	1	0	0.9935	0.9359	0.8873	0.9581
	M-HEMANGIOSARCOMA	6	4	3	1	0.7543	0.4481	0.5349	0.6039
LUNG	B-ADENOMA, BRONCHIOL	15	3	4	2	0.9188	0.9256	0.7298	0.9036
	M-CARCINOMA, BRONCHI	19	5	7	0	0.9949	0.8750	0.5013	0.9978
MUSCLE, SKELETA	M-FIBROSARCOMA	1	0	0	0	0.5634	0.3333	0.2941	0.2619
	M-HEMANGIOSARCOMA	0	0	0	1	0.1557	.	.	0.2640
PENIS	M-FIBROSARCOMA	0	1	0	0	0.3443	0.3413	.	.

(Continued)

**Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Male Mice**

(Continued)

Organ Name	Tumor Name	0 mg	50 mg	250 mg	600 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=60	High N=60	Dos Resp			
PINNA	B-PAPILLOMA, SQUAMOU	0	0	1	0	0.3443	.	0.2966	.
PITUITARY	B-ADENOMA	0	0	1	1	0.0826	.	0.2966	0.2640
SALIV GL, MANDI	M-CARCINOMA	1	0	0	0	0.5660	0.3360	0.2966	0.2640
SKIN	B-HISTIOCYTOMA	0	1	0	0	0.3443	0.3360	.	.
	B-PAPILLOMA, SQUAMOU	2	0	0	0	0.8105	0.5573	0.5035	0.4568
	M-FIBROSARCOMA	0	0	1	0	0.3443	.	0.3025	.
SPLEEN	B-HEMANGIOMA	1	2	0	0	0.7290	0.2682	0.2966	0.2640
	M-HEMANGIOSARCOMA	1	0	0	0	0.5660	0.3360	0.2966	0.2640
STOMACH, GL	B-ADENOMA	0	1	0	0	0.3443	0.3413	.	.
STOMACH, NONGL	B-PAPILLOMA, SQUAMOU	0	0	0	1	0.1557	.	.	0.2640
TESTIS	B-INTERSTITIAL CELL	2	0	0	0	0.8128	0.5609	0.5070	0.4599
	B-SERTOLI CELL TUMOR	1	0	0	0	0.5660	0.3360	0.2966	0.2640
THYMUS	M-HEMANGIOSARCOMA	0	0	1	0	0.3443	.	0.2966	.
TONGUE	B-PAPILLOMA, SQUAMOU	0	1	0	0	0.3443	0.3413	.	.
URINARY BLADDER	M-CARCINOMA, TRANSIT	0	0	0	1	0.1596	.	.	0.2698

**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice**

Organ Name	Tumor Name	0 mg	50 mg	250 mg	600 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=60	High N=60	Dos Resp			
ADIPOSE TISSUE	M-MESOTHELIOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
ADRENAL, CORTEX	B-ADENOMA	0	0	1	0	0.3927	.	0.3482	.
	B-ADENOMA, SUBCAPSUL	3	0	0	1	0.5491	0.7546	0.7271	0.4019
	M-CARCINOMA	2	0	0	0	0.8527	0.6020	0.5732	0.5495
ADRENAL, MEDULL	B-PHEOCHROMOCYTOMA	1	0	0	2	0.0947	0.3675	0.3451	0.2572
BONE, OTHER	M-OSTEOSARCOMA	0	1	0	0	0.3927	0.3707	.	.
CERVIX	B-LEIOMYOMA	0	2	1	0	0.5507	0.1354	0.3482	.
	B-POLYP, ENDOMETRIAL	1	2	1	0	0.6917	0.3088	0.5772	0.3303
	M-SARCOMA, ENDOMETRI	2	1	0	0	0.8442	0.3043	0.5732	0.5495
DUODENUM	M-CARCINOMA	0	0	0	1	0.1885	.	.	0.3303
GALLBLADDER	B-PAPILLOMA	0	0	0	1	0.1885	.	.	0.3303
HARDERIAN GLAND	B-ADENOMA	5	2	1	2	0.5708	0.5098	0.6780	0.4150
	M-CARCINOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
HEART	M-RHABDOMYOSARCOMA	0	1	0	0	0.3927	0.3707	.	.
HEMATO NEOPLASI	M-LYMPHOMA	19	5	13	7	0.5178	0.9188	0.3091	0.6806
	M-SARCOMA, HISTIOCYT	7	1	5	3	0.3728	0.8603	0.4251	0.4322
JEJUNUM	B-ADENOMA	1	0	0	0	0.6146	0.3675	0.3451	0.3273
LIVER	B-HEMANGIOMA	0	1	1	0	0.3831	0.3707	0.3482	.
	M-CARCINOMA, HEPATOC	0	1	0	0	0.3927	0.3707	.	.
	M-HEMANGIOSARCOMA	2	0	1	0	0.6853	0.6020	0.2732	0.5495

(Continued)

**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice**

(Continued)

Organ Name	Tumor Name	0 mg	50 mg	250 mg	600 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=60	High N=60	Dos Resp			
LUNG	B-ADENOMA, BRONCHIOL	15	5	5	4	0.8557	0.8366	0.7788	0.8355
	M-CARCINOMA	12	9	4	5	0.7346	0.3616	0.6944	0.5055
	M-OSTEOSARCOMA	0	1	0	0	0.3927	0.3707	.	.
MAMMARY, FEMALE	M-CARCINOMA	1	2	0	1	0.4367	0.3088	0.3482	0.5616
	M-FIBROSARCOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
MUSCLE, SKELETA	M-FIBROSARCOMA	2	1	1	1	0.4904	0.3043	0.2732	0.7078
OVARY	B-ADENOMA	0	0	1	0	0.3927	.	0.3482	.
	B-CYSTADENOMA	0	0	1	1	0.1121	.	0.3482	0.3303
	B-LUTEOMA	2	0	1	0	0.6886	0.6060	0.2774	0.5535
PANCREAS	B-ADENOMA, ISLET CEL	2	0	0	0	0.8527	0.6020	0.5732	0.5495
PITUITARY	B-ADENOMA	6	3	2	2	0.6744	0.4346	0.5651	0.5202
	M-CARCINOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
SKIN	B-KERATOACANTHOMA	0	0	1	0	0.3927	.	0.3482	.
	B-NEUROFIBROMA	0	0	0	1	0.1885	.	.	0.3303
	B-PAPILLOMA, SQUAMOU	1	0	0	0	0.6178	0.3707	0.3482	0.3303
	M-CARCINOMA, BASAL C	0	1	0	0	0.3927	0.3707	.	.
	M-CARCINOMA, SQUAMOU	1	0	0	0	0.6146	0.3675	0.3451	0.3273
	M-FIBROSARCOMA	1	0	1	0	0.4755	0.3707	0.5772	0.3303
SPLEEN	M-HEMANGIOSARCOMA	1	1	0	1	0.3897	0.6020	0.3451	0.5495
STOMACH, NONGL	B-PAPILLOMA, SQUAMOU	0	0	0	1	0.1885	.	.	0.3303
	M-SARCOMA, SPINDLE C	0	0	0	1	0.1885	.	.	0.3303
SUBCUTANEOUS TI	M-FIBROSARCOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
	M-RHABDOMYOSARCOMA	0	1	0	0	0.3927	0.3707	.	.

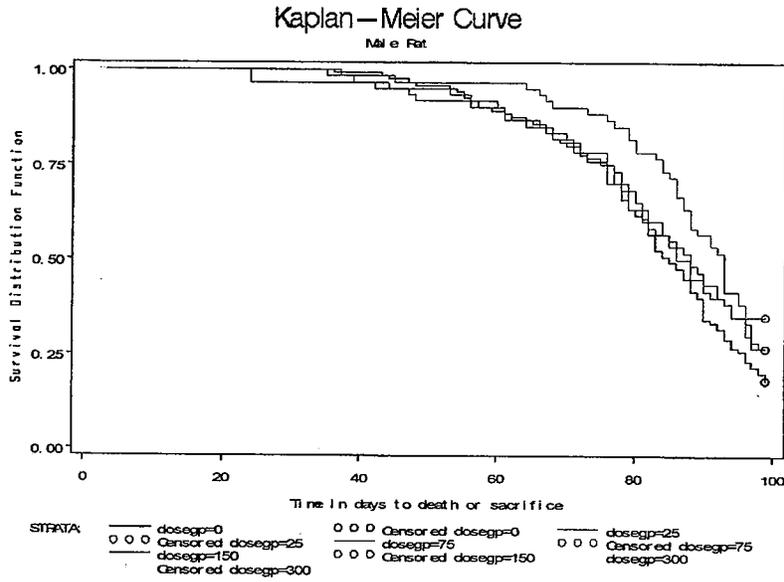
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**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice**

(Continued)

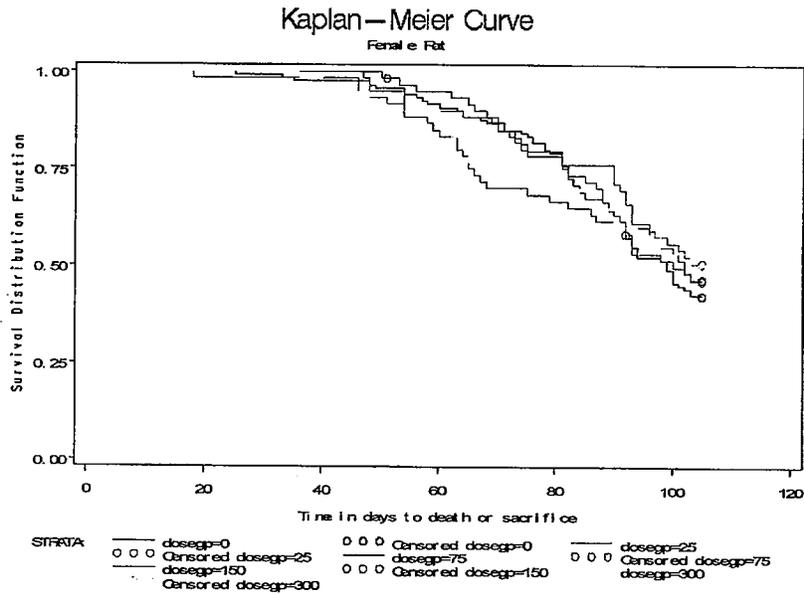
Organ Name	Tumor Name	0 mg	50 mg	250 mg	600 mg	P_Value	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=60	High N=60	Dos Resp			
THYROID	B-ADENOMA, FOLLICULA	3	0	0	0	0.9442	0.7508	0.7231	0.6996
UTERUS	B-HEMANGIOMA	0	2	0	0	0.6324	0.1354	.	.
	B-LEIOMYOMA	1	0	0	0	0.6178	0.3707	0.3482	0.3303
	B-POLYP, ENDOMETRIAL	4	3	1	1	0.7771	0.5098	0.5655	0.5299
	M-ADENOCARCINOMA	0	0	1	0	0.3927	.	0.3482	.
	M-SARCOMA, ENDOMETRI	5	6	1	4	0.4393	0.1962	0.6840	0.3534

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
Male Rats



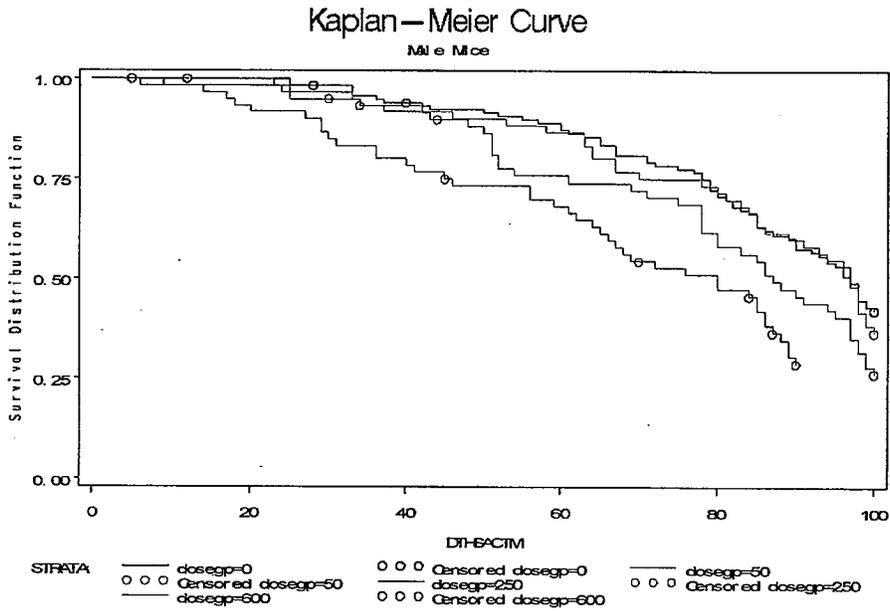
X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



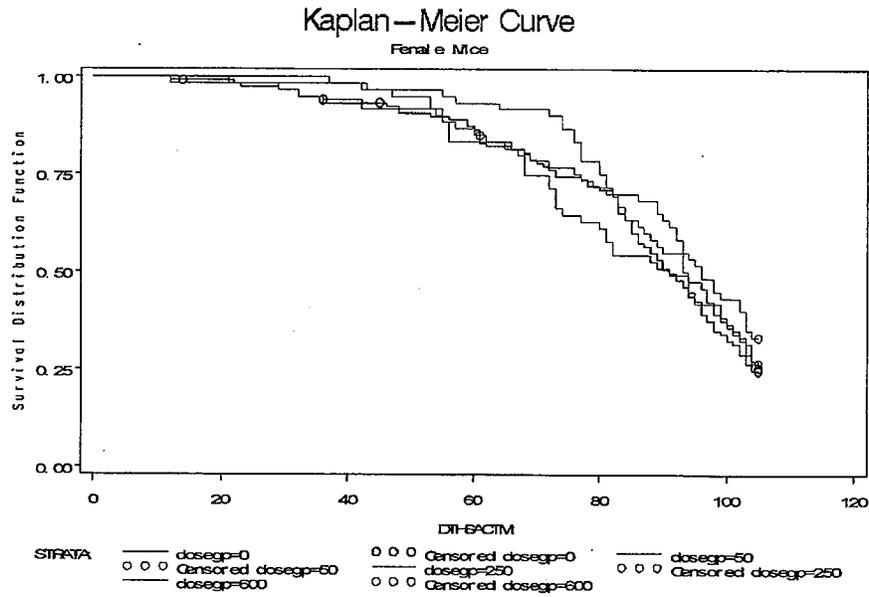
X-Axis: Weeks, Y-Axis: Survival rates

Figure 2A: Kaplan-Meier Survival Functions for Male Mice
Male Mice



X-Axis: Weeks, Y-Axis: Survival rates

Figure 2B: Kaplan-Meier Survival Functions for Female Mice
Female Mice



X-Axis: Weeks, Y-Axis: Survival rates

**7A: Dose Response Relationship Test and Pairwise Comparisons Using All Dose Groups
Male Rat**

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	300 mg	P_Value				
		Cont N=120	Low N=60	Mid-Low N=60	Mid-Hi N=60	High N=60	Dos Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	P_Value C vs. H
Adrenal, Cortex	B-Adenoma	11	3	3	3	1	0.8668	0.8277	0.7541	0.7681	0.7211
	M-Carcinoma	1	1	0	0	0	0.7294	0.6100	0.3419	0.3419	0.1942
Adrenal, Medull	B-Pheochromocytoma	23	15	7	6	0	0.9997	0.4519	0.8680	0.9258	0.9958
Body, Whole/Cav	M-Hemangiosarcoma	1	0	1	1	0	0.4482	0.3689	0.5761	0.5688	0.1942
	M-Histiocytic Sarcom	0	1	0	2	0	0.2475	0.3770	.	0.1169	.
	M-Lrg Granular Cell	1	0	0	0	0	0.6352	0.3689	0.3419	0.3419	0.1942
	M-Lymphosarcoma	5	1	0	0	0	0.9908	0.7303	0.8821	0.8821	0.6663
Brain	B-Granular Cell Tumo	0	0	1	1	0	0.2644	.	0.3448	0.3448	.
	M-Malignant Astrocyt	1	1	0	0	0	0.7288	0.6100	0.3419	0.3419	0.1942
	M-Malignant Oligoden	1	0	0	0	0	0.6352	0.3719	0.3448	0.3448	0.1942
	M-Meningeal Sarcoma	2	0	0	0	0	0.8677	0.6036	0.5688	0.5688	0.3519
Cavity, Abdomin	B-Lipoma	0	0	1	0	0	0.4463	.	0.3448	.	.
Eye	M-Fibrosarcoma	1	0	0	0	0	0.6352	0.3689	0.3419	0.3419	0.1942
GI, Zymbal's	M-Carcinoma	2	0	0	1	0	0.5597	0.6036	0.5688	0.2689	0.3519
Jejunum	M-Carcinoma	0	0	1	0	0	0.4463	.	0.3448	.	.
	M-Fibrosarcoma	0	0	0	1	0	0.2671	.	.	0.3448	.
Kidney	M-Malignant Renal Me	0	1	0	0	0	0.4463	0.3770	.	.	.
	M-Nephroblastoma	0	0	0	1	0	0.2695	.	.	0.3504	.
Liver	B-Adenoma, Hepatoce	2	1	0	1	0	0.6444	0.3063	0.5688	0.2689	0.3519
Pancreas	B-Adenoma, Acinar Ce	1	0	1	1	0	0.4478	0.3719	0.5727	0.5727	0.1942
	B-Adenoma, Islet Cel	4	0	2	0	0	0.9045	0.8459	0.3340	0.8175	0.5829
	M-Carcinoma, Islet C	0	1	0	0	0	0.4463	0.3770	.	.	.

(Continued)

**7A: Dose Response Relationship Test and Pairwise Comparisons Using All Dose Groups
Male Rat**

(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	300 mg	P_Value				
		Cont N=120	Low N=60	Mid-Low N=60	Mid-Hi N=60	High N=60	Dos Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	P_Value C vs. H
Parathyroid	B-Adenoma	0	0	0	1	0	0.2671	.	.	0.3448	.
Pituitary	B-Adenoma	14	10	6	4	2	0.9079	0.3816	0.5493	0.7894	0.6400
Skin	B-Fibroma	1	0	1	1	0	0.4478	0.3719	0.5727	0.5727	0.1942
	B-Keratoacanthoma	4	0	0	2	0	0.6764	0.8429	0.8141	0.3281	0.5829
	M-Fibrosarcoma	2	0	1	0	0	0.7610	0.6074	0.2806	0.5727	0.3519
	M-Malignant Basal Ce	0	0	1	0	0	0.4463	.	0.3448	.	.
	M-Sarcoma	0	1	0	0	0	0.4463	0.3770	.	.	.
Skin/Subq, Othe	B-Keratoacanthoma	7	0	0	1	0	0.9706	0.9615	0.9483	0.8189	0.7877
	B-Papilloma, Squamou	1	1	2	0	0	0.6444	0.6139	0.2729	0.3448	0.1942
	M-Carcinoma, Basal C	0	1	0	0	0	0.4463	0.3719	.	.	.
	M-Fibrosarcoma	2	0	0	0	0	0.8677	0.6036	0.5688	0.5688	0.3519
Stomach, Nongl	M-Carcinoma, Squamou	0	1	0	0	0	0.4463	0.3719	.	.	.
Tail	B-Keratoacanthoma	2	2	3	1	0	0.6776	0.4803	0.2185	0.2689	0.3519
Testis	B-Interstitial Cell	1	0	0	2	0	0.3346	0.3719	0.3448	0.2729	0.1942
Thyroid	B-Adenoma, C-cell	13	17	11	11	3	0.5674	0.0138	0.1347	0.1347	0.3773
	M-Carcinoma, C-cell	1	1	0	0	0	0.7294	0.6074	0.3448	0.3448	0.1942
Urinary Bladder	M-Carcinoma, Transit	0	1	0	0	0	0.4463	0.3719	.	.	.

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
(Using Controls, Low, Mid-Low and Mid-High)
Female Rats**

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	P_Value			
		Cont N=120	Low N=60	Mid-Low N=60	Mid-High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH
fff									
Adrenal, Cortex	B-Adenoma	9	5	6	6	0.2601	0.5202	0.4200	0.3508
	M-Carcinoma	0	0	2	1	0.1187	.	0.1163	0.3228
Adrenal, Medull	B-Pheochromocytoma	3	2	1	4	0.1080	0.5417	0.4257	0.1512
	M-Malignant Pheochro	0	0	1	0	0.4000	.	0.3435	.
Body, Whole/Cav	B-Hemangioma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
	M-Hemangiosarcoma	0	1	0	0	0.4000	0.3333	.	.
	M-Histiocytic Sarcom	0	0	1	0	0.4000	.	0.3435	.
	M-Lrg Granular Cell	2	0	0	0	0.8411	0.5573	0.5708	0.5432
	M-Lymphosarcoma	2	0	0	1	0.5586	0.5573	0.5708	0.6930
	M-Malignant Mesothel	0	0	0	1	0.1944	.	.	0.3281
Cavity, Abdomin	B-Lipoma	0	0	0	1	0.1907	.	.	0.3228
Cervix	B-Polyp, Endometrial	3	1	2	1	0.4924	0.4166	0.5619	0.3885
	M-Carcinoma	1	1	0	0	0.6804	0.5573	0.3435	0.3228
Duodenum	B-Fibroma	0	0	0	1	0.1907	.	.	0.3228
	M-Sarcoma	0	0	0	1	0.1907	.	.	0.3228
Eye	M-Fibrosarcoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Heart	M-Endocardial Schwan	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Kidney	M-Fibrosarcoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Liver	B-Adenoma, Hepatocel	6	1	1	0	0.9743	0.7440	0.7623	0.9090
Mammary, Female	B-Adenoma	2	0	0	1	0.5586	0.5573	0.5708	0.6930
	B-Fibroadenoma	60	23	20	13	0.9998	0.9266	0.9789	0.9995
	M-Carcinoma	15	2	0	3	0.9765	0.9620	0.9985	0.8809

(Continued)

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
(Using Controls, Low, Mid-Low and Mid-High)
Female Rats**

(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	P_Value	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH
		Cont N=120	Low N=60	Mid-Low N=60	Mid-High N=60	Dose Resp			
fff									
Mammary, Female	M-Fibrosarcoma	0	0	1	0	0.4000	.	0.3435	.
	M-Sarcoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
	M-Schwannoma	0	0	1	0	0.4000	.	0.3435	.
Muscle, Other	M-Schwannoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Nerve, Other	M-Malignant Schwanno	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Ovary	B-Luteoma	0	1	0	0	0.4000	0.3333	.	.
	M-Malignant Granulos	0	0	2	0	0.3888	.	0.1163	.
Pancreas	B-Adenoma, Islet Cel	5	1	1	3	0.3888	0.6541	0.6740	0.5084
	M-Carcinoma, Islet C	0	1	0	0	0.4000	0.3333	.	.
Pituitary	B-Adenoma	67	27	21	17	0.9996	0.8786	0.9902	0.9989
	M-Carcinoma	0	1	1	1	0.1673	0.3333	0.3435	0.3228
Skin	B-Fibroma	1	0	1	0	0.4729	0.3333	0.5708	0.3228
	M-Fibrosarcoma	0	1	0	0	0.3981	0.3385	.	.
	M-Leiomyosarcoma	0	0	1	0	0.4000	.	0.3435	.
Skin/SubQ, Othe	B-Basal Cell Tumor	1	0	0	0	0.6000	0.3333	0.3435	0.3228
	B-Keratoacanthoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
	B-Papilloma, Squamou	0	0	1	0	0.4000	.	0.3435	.
	M-Carcinoma, Basal C	0	1	0	0	0.4000	0.3333	.	.
	M-Fibrosarcoma	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Stomach, Nongl	M-Carcinoma, Squamou	1	0	0	0	0.6000	0.3333	0.3435	0.3228
Tail	M-Leiomyosarcoma	0	0	1	0	0.4000	.	0.3435	.
Thymus	B-Adenoma	0	0	0	1	0.1907	.	.	0.3228

(Continued)

**Table 7B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
(Using Controls, Low, Mid-Low and Mid-High)
Female Rats**

(Continued)

Organ Name	Tumor Name	0 mg	25 mg	75 mg	150 mg	P_Value				
		Cont N=120	Low N=60	Mid-Low N=60	Mid-High N=60	Dose Resp	P_Value C vs. L	P_Value C vs. ML	P_Value C vs. MH	
fff										
Thyroid	B-Adenoma, C-cell	28	22	11	10	0.9398	0.0344	0.7492	0.7665	
	M-Carcinoma, C-cell	0	1	2	1	0.1574	0.3333	0.1163	0.3228	
uterus	B-Polyp, Endometrial	39	11	13	11	0.9531	0.9673	0.9311	0.9423	
	M-Carcinoma	2	0	2	1	0.3684	0.5573	0.4257	0.6930	
	M-Carcinoma, Squamou	1	0	0	3	0.0336	0.3333	0.3435	0.1030	
	M-Sarcoma, Endometri	1	0	0	0	0.6000	0.3333	0.3435	0.3228	
Vagina	B-Polyp, Endometrial	0	0	0	1	0.1907	.	.	0.3228	

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OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Design of Experiment Studies

NDA/Serial Number:	22-350/000
Drug Name:	Saxagliptin Tablets
Indication:	Type 2 Diabetes
Applicant:	Bristol Myers Squibb
Date:	October 30, 2007
Classification:	Standard
Statistical Reviewer:	Roswitha Kelly, M.S., OTS/OB/DB6
Concurring Reviewer:	Yi Tsong, Ph.D., OTS/OB/DB6
Medical Division:	Division of Metabolism and Endocrine Products
Chemistry Reviewer:	Prafull Shiromani, Ph.D., OPS/ONDQA/DPA1
Chemistry Branch Chief:	Ali Al-Hakim, Ph. D., OPS/ONDQA/DPA
Project Manager:	Rachel Hartford, OND/ODEII/DMEP

Keywords: Saxagliptin Tablets, Design of Experiment

Distribution: NDA 22-350/Saxagliptin Tablets
OND/ODEII/DMEP/R. Hartford
ONDQA/P. Shiromani, Ph.D./A. Al-Hakim, Ph.D.
OTS/OB/DB6/R. Kelly/Y. Tsong, Ph.D./S. Machado, Ph.D.
OTS/OB/E. Nevius, Ph.D./R. Tiwari, Ph.D./L. Patrician, M.S.

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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The reviewer had been requested by the reviewing chemist to evaluate the sponsor's designs of experiments (DOE) on which they planned to base their commercial manufacturing process. The reviewer could not reproduce any of the statistics employed by the sponsor and a letter requesting clarification was sent. In their response to this letter, the sponsor clarified their usage of statistical terms. Though from a purely statistical point of view this usage may be judged liberal, the sponsor clarified all issues with the exception of a few remaining errors which could be typographical. The sponsor's conclusion that the observed DOE results are indistinguishable from the product quality obtained under commercial manufacture has not been formally substantiated in this submission. The reviewer and Dr. Shiromani, the reviewing chemist, discussed the sponsor's response and agreed that it is adequate and acceptable.

1.2. Brief Overview of the Designs of Experiments

In the original submission the sponsor presented the design and results of two experiments. The first design came out of much process development and was to determine the design space for the commercial manufacture of Saxagliptin. The second design was to confirm that the critical impurity was adequately controlled. Based on the DOE results the sponsor concluded that the design space for the manufacture of the drug substance has been substantiated.

1.3. Statistical Issues and Findings

In the original submission of the designs and results of the sponsor's experiments, the reviewer could not reproduce any of the sponsor's findings. Further, certain statistics, which the sponsor presumably had performed, could not be found. Hence clarification was requested from the sponsor. The sponsor explained that these statistics, such as two-way interactions and correlation coefficients, were not actually calculated. The non-significant two-way interactions were deduced from the non-significant main effects and the fact that main effects and two-way interactions were confounded. The use of 'non-significant correlation' between the factors and the dependent variables reflected the fact that the regression term for each main effect was non-significant. These clarifications are statistically correct, even though some more detail in the original submission could have saved time. Other confusions could be attributed to typographical errors in numbers.

2. INTRODUCTION

2.1. Overview

The sponsor submitted the design and analysis results of $\frac{1}{4}$ of a 2^5 full factorial with four center points, i.e. twelve 5-factor experiments to establish the design space for the manufacture of Saxagliptin and a full 2^3 factorial design with four center points (again twelve experiments) to establish the design space for the conversion of

(b)(4)

2.2. Data Sources

According to the sponsor the levels of the design factors were determined after much process development. These factors and the fractional factorial model led to output variables with small variances and therefore these design factors will be employed in the commercial manufacturing process. As such, no further data are required.

3. STATISTICAL EVALUATION

In the sponsor's original submission of their DOE approach, the reviewer could not reproduce any of their results in part due to insufficient detail. For example, each factor was reported as non-significant but none of the model estimates for the factors were given. Further the sponsor stated that 'there are no two-factor interactions that were overlooked during initial process development' and 'no significant two-factor interactions between the parameters were uncovered'. From these statements the reviewer assumed that the model or a previous model had contained two-way interactions, which were not reported. In their response, the sponsor clarified that two-way interactions were confounded with main effects (for the first DOE model) and were assumed to be non-significant because the main effects were found to be non-significant. In the second DOE model (only 3 factors) they submitted the two-way interactions which had been modeled and found to be non-significant. These responses are statistically correct. Similarly, the original submission contained the sentence '... analysis of the reaction yield with respect to the input parameters revealed no statistical correlation between the input and output variables as indicated by a comparison of the calculated individual t-ratios with the critical t-ratio of ...'. The reviewer found this statement implying that actual correlation coefficients were calculated. In addition she could not verify the t-ratio because the model estimates for each factor and their standard deviation were not provided and a minor typographical error in the critical t-ratio raised further doubts. In their response to our request for clarification, the sponsor stated that this statement meant that there was no significant effect of the factors on yield, the dependent variable, and corrected the critical value for the t-ratio.

In the sponsor's response to our request for clarification are still some typographical errors which could be confusing: Their fractional factorial design is stated to be 'a $\frac{1}{4}$ replication of a 2_5 full factorial...' which should be reported as a $\frac{1}{4}$ of a 2^5 full factorial design. The second design was again reported as a full 2_3 factorial design, not a full 2^3

design. There is also a sentence referring to the 3-factor DOE: 'The two way interactions are correlated with the main effects, none of which are statistically significant.' The sponsor presumably meant: ... two-way interactions are confounded with the main effects....

In their response to Question 9, the sponsor stated that (italics added by reviewer) 'The quality of the drug substance in each of these experiments is *indistinguishable* from the quality of the drug substance produced at commercial manufacturing scale. ...Based on the DOE results and the *alignment* between the DOE and commercial manufacturing batch quality, BMS believes that the design space proposed for the drug substance manufacture has been *substantiated*.' The reviewer does not know how the sponsor compared the quality of the drug substance shown in these DOE experiments and in the commercial manufacture. It is presumed that the observed small variability in the output variables of the DOE experiments is similar to the one observed in the commercially manufactured product. However, apparently no formal statistical comparison procedure was used.

4. CONCLUSION

Overall, the sponsor has satisfactorily answered all questions and concerns and their DOE approach provided them with the confirmation that the design factors have no significant effect on the dependent variables. However, their conclusions that their DOE results are indistinguishable from the batch quality obtained under commercial manufacturing has not been established by any statistical method that was part of this submission. These findings were discussed with the review chemist, Dr. Shiromani.

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