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SAXAGLIPTIN
April 1, 2009

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

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Forum: Endocrinologic and Metabolic Drugs Advisory Committee meeting

Topic: April 1, 2009: NDA 22-350 - Saxagliptin (Bristol Myers Squibb)

INTRODUCTION

On July 1 and 2, 2008, the Food and Drug Administration (FDA) convened a public advisory committee meeting to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus. The advisory panel was populated by the Endocrinologic and Metabolic Drugs Advisory Committee, diabetologists, cardiologists, statisticians, and members of the Drug Safety and Risk Management Committee (DSARM). The committee was asked to vote on the following question:

“It should be assumed that an anti-diabetic therapy with a concerning CV [cardiovascular] safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?”

Fourteen panel members voted “yes” to this question and two voted “no”. The transcript is available at <http://www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic>.

After considering the discussion at this meeting as well as other available data, FDA determined that cardiovascular safety of therapies developed for type 2 diabetes should be more thoroughly evaluated during drug development. Therefore, in December 2008, FDA issued a final guidance for industry titled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, a copy of which is included in this background package.

In this guidance, FDA reaffirmed that HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication for glycemic control. However, FDA acknowledged that diabetes is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. FDA stated that the absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. However, for type 2 diabetes, FDA noted that the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

Therefore, this guidance asks sponsors to demonstrate that new therapies for type 2 diabetes do not result in an unacceptable increase in cardiovascular risk. This guidance does not address cardiovascular assessment of already-approved treatments for type 2 diabetes, which will be addressed in a future guidance.

Specifically, this guidance asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events (e.g., cardiovascular death, myocardial infarction, and stroke) during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of major cardiovascular events can reliably be performed. The sponsor should provide a protocol describing the statistical methods for the proposed meta-analysis of all placebo-controlled trials, add-on trials, and active-comparator trials. The guidance states that it is likely that the controlled trials will need to last longer than the typical 3-6 months duration to obtain a sufficient number of events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.
- To enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a cardiovascular standpoint, the sponsor should compare the incidence of major cardiovascular events with the investigational agent to the incidence of the same types of events occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

FDA has publically communicated that all new unapproved therapies for type 2 diabetes (even pending new drug applications submitted to FDA prior to issuance of the final diabetes cardiovascular guidance) will be held to the standards of this guidance.

SAXAGLIPTIN ADVISORY COMMITTEE MEETING

FDA has convened an advisory committee meeting on April 1, 2009, to discuss the pending new drug application for saxagliptin, which is seeking an indication for the treatment of type 2 diabetes. The Phase 2 and 3 clinical trials for this application were designed and completed well in advance of the final guidance being issued. Despite not having a prospective plan for cardiovascular risk assessment, FDA and the applicant have strived to objectively characterize cardiovascular risks for this therapy. The goal of the advisory committee meeting is to discuss whether the saxagliptin new drug application sufficiently meets the December 2008 diabetes cardiovascular guidance, with respect to meeting the upper bound of the two-sided 95% confidence interval of 1.8, to support approvability.

SAXAGLIPTIN: MECHANISM OF ACTION

Saxagliptin is a glucagon-like peptide (GLP)-1-based pharmacologic therapy for type 2 diabetes. GLP-1 stimulates glucose-dependent insulin release, slows gastric emptying, inhibits inappropriate post-meal glucagon release, and reduces food intake. GLP-1 concentrations are reduced in patients with type 2 diabetes but cannot be supplemented by unmodified GLP-1 because of the short half-life (<2 minutes) due to rapid degradation by the dipeptidyl peptidase (DPP)-4 enzyme. Therefore, GLP-1-based therapies for type 2 diabetes either inhibit DPP-4 to slow the degradation of endogenous GLP-1 or involve administration of pharmacological doses of modified GLP-1 that is resistant to DPP-4 degradation.

Saxagliptin is an oral DPP-4 inhibitor. Currently, there is one FDA-approved DPP-4 inhibitor known as Januvia (sitagliptin phosphate). Both saxagliptin and Januvia are dosed once-daily.

IMPORTANT CONSIDERATIONS

The saxagliptin new drug application was received by FDA on June 30, 2008 prior to the July 2008 advisory committee meeting that was convened to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. Therefore, the saxagliptin program was not prospectively designed to assess cardiovascular risk. Instead, the sponsor and FDA performed post-hoc evaluation of cardiovascular events (see below). There were no pre-specified definitions or prospective adjudication of major cardiovascular events and, because of the retrospective nature of these analyses, some events have insufficient information to definitively determine whether a cardiovascular event of interest occurred.

POST-HOC ANALYSES OF CARDIOVASCULAR EVENTS

After submission of the saxagliptin new drug application, the FDA requested that the sponsor perform post-hoc analyses of cardiovascular events. The analyses that were requested by FDA

are described in more detail in the joint clinical and statistical review documents prepared by FDA reviewers. An overview is provided here.

FDA requested that the main cardiovascular analysis be conducted on the randomized, controlled periods for all completed phase 2 and phase 3 clinical trials. An additional analysis included blinded, controlled data from treatment periods that extended beyond the timepoint of the primary efficacy endpoint for glycemic control.

The cardiovascular endpoints requested by FDA are based on “MedDRA” and “Standardised MedDRA Queries” (SMQs). A brief description of these methodologies is presented here as background. MedDRA, which stands for “Medical Dictionary for Regulatory Activities”, was developed by the International Conference on Harmonisation (ICH) and is used by regulatory authorities and sponsors to code adverse events reported in clinical trials and postmarketing databases. Because investigators can report the same adverse event in many different ways, it would be difficult to rely only on these verbatim investigator-reported terms for tabulating the incidence of various adverse events. Coders who are trained in the use of MedDRA review the verbatim terms reported by investigators and match these verbatim terms to one of over 65,000 “Lowest Level Terms (LLTs)”. Each LLT is linked to a single “Preferred Term” (PT). For example, LLTs of “arrhythmia”, “dysrhythmias”, and “arrhythmia not otherwise specified” would all be linked to the single PT of “arrhythmia”. Analyses of adverse events are then performed using PTs, which represent single medical entities.

The size and complexity of MedDRA terminology may result in different users selecting different sets of PTs when trying to retrieve cases related to a particular safety issue. SMQs for a wide variety of medical conditions of interest have been developed in an attempt to standardize the sets of PTs that should be included when evaluating a particular safety issue. An SMQ is a grouping of PTs that are potentially related to a defined medical condition of interest. For example, in MedDRA version 11.1, the “Myocardial Infarction” SMQ contains 30 preferred terms (e.g., “acute coronary syndrome”, “coronary artery occlusion”, “silent myocardial infarction”, “blood creatine phosphokinase increased”). Therefore, patients who were reported to have experienced any of these 30 preferred terms would be counted as having had a myocardial infarction in this SMQ. Although some of these preferred terms could be consistent with myocardial infarction, there may be an alternate explanation in some patients. For example, “blood creatine phosphokinase increased” could be related to exercise, muscle trauma, medications, or a variety of other causes. Therefore, the SMQ analyses will detect all patients with reported PTs that could be consistent with, but not necessarily diagnostic of, the condition of interest.

FDA requested that the sponsor use two endpoints for the cardiovascular analyses. The first endpoint, called “SMQ MACE”, was defined as a composite endpoint of cardiovascular death and all preferred terms in the Standardised MedDRA Queries (SMQs) for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents.” A second endpoint, called “Custom MACE”, was also analyzed. The “Custom MACE” endpoint is a subset of “SMQ MACE” and is considered to be more specific than “SMQ MACE” for the reasons explained above.

The “Custom MACE” was created as follows. Without considering which events had actually occurred, a panel of 3 FDA clinical reviewers independently reviewed the list of all PTs included in the “SMQ MACE” with the following question in mind: “If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?” The goal was to select only those PTs that seemed highly likely to represent true events of myocardial infarction or stroke with a mechanism of atherosclerotic plaque development followed by plaque rupture or thrombosis (as opposed to events with non-atherosclerotic mechanisms, such as rupture of a congenital aneurysm). The lists generated by the 3 clinical reviewers were compared and any PTs for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached regarding inclusion or exclusion for all PTs. FDA acknowledges that this post-hoc approach is imperfect – some events have insufficient information to definitively assess whether an endpoint of interest occurred and other reasonable physicians may have chosen a different set of PTs for the “Custom MACE” endpoint. A listing of the PTs included in the “SMQ MACE” and “Custom MACE” endpoints as well as the results of the requested cardiovascular analyses are shown in FDA’s clinical/statistical review of saxagliptin.

The cardiovascular risk analyses, based on both “SMQ MACE” and “Custom MACE”, are presented in the FDA background materials. Because both analyses are *post hoc*, there is no conclusion that one set of preferred terms is superior to the other. Rather, FDA reviews attempt to explain how use of certain preferred terms may contribute to differences in point estimates for cardiovascular risk and the accompanying confidence intervals or to highlight how different analyses might still yield consistent findings.

CONTENTS OF THE FDA BACKGROUND PACKAGE

This FDA background package contains:

- This introductory document
- Joint clinical/statistical review of major cardiovascular events in the saxagliptin phase 2/3 program
- Non-clinical pharmacology/toxicology review of cardiovascular findings in animals
- The February 2007 draft guidance for industry entitled *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*
- The December 2008 final guidance for industry entitled *Diabetes Mellitus -- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*

CONCLUSIONS

Type 2 diabetes affects millions of people in the United States, causing considerable morbidity and mortality. Cardiovascular disease accounts for most deaths among people with diabetes. Therefore, the question of cardiovascular safety for new drugs developed for the treatment of type 2 diabetes, such as saxagliptin, is of high public health importance. We look forward to a thorough and reasoned discussion of this topic. Thank you in advance for your recommendations and for the vital public health contribution you are making through your participation in this important meeting.

Non-clinical cardiovascular Risk Assessment of saxagliptin for Advisory Committee Briefing Document

NDA 22-350

Drug: Saxagliptin, a dipeptidyl peptidase 4 inhibitor

Toxicology Reviewer: Fred Alavi, Ph.D.

Toxicology Supervisor: Todd Bourcier, Ph.D.

Advisory Committee Meeting Date: April 1, 2009

A comprehensive review of preclinical data did not uncover evidence of cardiac toxicities indicative of human risk. Saxagliptin had no significant effect on potassium channel current in the hERG assay or on conduction kinetics in rabbit Purkinje fibers at concentrations up to 30 μ M (\geq 200 fold maximum clinical drug concentration). Single oral doses of saxagliptin administered to conscious telemetered dogs and to monkeys did not significantly alter blood pressure and heart rate or produce electrocardiographic abnormalities at drug concentrations in excess of 100-fold the maximum clinical concentration from a 5mg dose.

The general toxicology of saxagliptin was evaluated in rats, mice, dogs, and monkeys. All species generated and were exposed to the active metabolite BMS-510849. Findings indicative of cardiovascular toxicity were not observed in any animal model based on the absence of significant changes in electrocardiograph data, terminal organ weights (including heart weight), or gross or histological pathology of a large panel of tissues. A transient decrease in blood pressure in rats during a 6 month study was judged unrelated to drug treatment (based on gender specificity and ancillary toxicity), as was a transient increase in heart rate in dogs during a 12 month study (based on transiency and lack of dependence on exposure). Edema, pleural effusions, and cardiac-related deaths observed in animals administered PPAR gamma agonist compounds were not observed with saxagliptin which targets a different molecular mechanism. Exposure to saxagliptin/active metabolite not associated with cardiovascular toxicity in animals was approximately 23x/11x (3-month monkey), 1000x/300x (lifetime mouse), 43x/11x (12-month dog), and 2000x/68x (lifetime rat) the mean human exposure (AUC) at the maximum recommended human dose of 5 mg/day.

While the preclinical data do not predict overt cardiovascular toxicity of saxagliptin in human subjects, it is important to note that healthy animals in relatively small numbers are used in standard toxicology studies. The animals have no co-morbidities such as hypertension, elevated cholesterol or triglycerides, or obesity that contribute to cardiovascular risks in diabetic patients. These factors require consideration when extrapolating cardiovascular risk from the preclinical data to the target patient population.

Joint Clinical and Statistical Briefing Document
Endocrinologic and Metabolic Drugs Advisory Committee Meeting

New Drug Application Number: 22-350

Drug Name: Onglyza® (saxagliptin tablets)

Indication: Type 2 Diabetes Mellitus

Applicant: Bristol-Myers Squibb Company (BMS)

AC Meeting Date: April 1, 2009

Medical Officer: Naomi Lowy, M.D.

Medical Division: Division of Metabolism and Endocrinology Products

Statistician: Joy Mele, M.S.

Biometrics Division: Division of Biometrics 2

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INTRODUCTION

Onglyza® (saxagliptin) is an oral dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), the incretin hormones. Incretin hormones are gut hormones that increase insulin secretion in response to enteral glucose challenge, regulating postprandial glucose excursion in a glucose-dependent manner, which mitigates the risk of hypoglycemia. In addition to enhanced postprandial insulin release, GLP-1 also reduces glucagon release from pancreatic α -cells, thereby reducing hepatic glucose production. This effect is also glucose-dependent, thereby contributing to the potential advantage of this drug class to avoid hypoglycemia. Saxagliptin is intended to be taken as a once-daily tablet.

With a New Drug Application (NDA) submitted June 30, 2008, Bristol-Myers Squibb Company is seeking an indication for saxagliptin as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

The primary focus of this document, prepared for the April 1, 2009 meeting of the Endocrine and Metabolic Drugs Advisory Committee, is to summarize the results of several analyses of major adverse cardiovascular events (MACE). One of the goals of the analyses is to address the issues raised by a guidance entitled “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” released by the FDA after the submission of the saxagliptin application. Before presenting those results, the studies analyzed are briefly described.

OVERVIEW OF SAXAGLIPTIN DEVELOPMENT PROGRAM

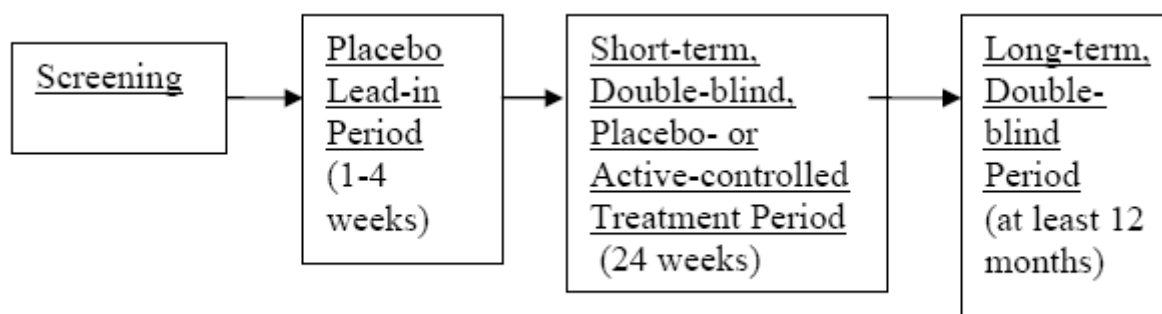
As of the time of the NDA submission, there were 26 completed Phase 1 and Phase 2 Trials (see Appendix 1 for listing). These trials were not included in the safety database used to assess cardiovascular risk because the studies were uncontrolled, conducted in healthy subjects, not randomized, or of short duration (see listing for more details). In addition, there were 11 Phase 2b/3 studies that have been completed or are ongoing. Three of these 11 are ongoing Phase 3b studies, for which no data have yet been submitted to FDA. The Phase 2b/3 program included in the NDA is comprised of the remaining 8 studies. These eight included one 12-week Phase 2b dose-finding study, one 12-week Phase 2 mechanism of action study, and six Phase 3 studies. These six are referred to as the Core Phase 3 studies. As of the time of the NDA submission, the long-term (LT) periods of the Core Phase 3 Studies were ongoing. Data from these long-term periods were included in both the original NDA and in the 120-Day Safety Update of the Clinical Safety Report. The Phase 2b/3 studies, the focus of the MACE analyses, are further detailed in Table 1 of the following section.

STUDY DESIGNS

Table 1 on the following page summarizes the designs of the 8 Phase 2b/3 studies which form the database for the MACE analyses described here. Six of the 8 studies were the Core Phase 3 studies, which include 2 monotherapy studies (CV181011 and CV181038), 3 add-on combination therapy studies (CV181014, CV181013 and CV181040), and 1 initial combination therapy study (CV181039). The two additional Phase 2b/3 studies (Studies CV181008 and CV181041), although included in all safety analyses, are not described in detail regarding patient disposition and rescue, because the contribution of these trials to the database was limited based on sample size or trial duration.

In the 6 Core Phase 3 studies, three doses of saxagliptin (2.5, 5, and 10 mg) were evaluated using a design depicted in Figure 1. After a placebo lead-in period, patients were randomized and followed for 24 weeks in the short-term period (ST). After the 24-week ST period, subjects were eligible to remain on randomized, double-blind treatment continuing into a voluntary long-term (LT) extension of at least 12 months. Subjects were eligible to enter the LT period either by completing all visits without requiring rescue in the ST period or meeting glycemic rescue criteria at any time in the ST period. The primary efficacy endpoint was the same in all the Core Phase 3 studies: the change in hemoglobin A1c (also known as HbA1c or A1c) from baseline to Week 24. If no Week 24 assessment was available, the last post-baseline measurement prior to Week 24 and before rescue was used. Results for the primary efficacy endpoint are not provided in this document.

Figure 1 Core phase 3 Study Design Overview



Source: Applicant's Summary of Clinical Efficacy, Figure 1.2.2

Table 1. Overview of Phase 2b and 3 Studies					
Study Phase Subjects Treated	Target Population/ A1c at Screening	ST Treatment Groups	LT Treatment Groups	Rescue Treatment	Duration (Weeks) ST/LT/Total
Monotherapy					
CV181011 Phase 3 N=401 (+66 received Saxa 10 mg OL)	Treatment naïve subjects (7-10% DB); (10-12% OL)	<u>4 Groups:</u> Saxa (2.5, 5, and 10 mg) or Placebo OL: Saxa 10mg	<u>4 Groups:</u> Saxa (2.5, 5, and 10 mg) or Placebo + DB Met 500 mg OL: Saxa 10 mg	Met 500 mg (titratable to 2000 mg)	24/182/206
CV181038 Phase 3 N=365	Treatment naïve subjects (7-10%)	<u>5 Groups:</u> Saxa (2.5 mg qam, 2.5/5 mg qam, 5 mg qam, and 5 mg qpm) or Placebo	<u>5 Groups:</u> Saxa (2.5 mg qam, 2.5/5 mg qam, 5 mg qam, and 5 mg qpm) or Placebo + DB Met 500 mg (Saxa could be titrated to 10 mg per protocol)	Met 500 mg (titratable to 2000 mg)	24/52/76
Add-on Combination Therapy					
CV181014 Phase 3 N=743	Met failure subjects: (Met 1500-2550 mg TDD) (7-10%)	<u>4 Groups:</u> OL Met + Saxa (2.5, 5, and 10 mg) or Placebo	<u>4 Groups:</u> OL Met + Saxa (2.5, 5, and 10 mg) or Placebo	Pioglitazone 15 mg (titratable to 30 or 45 mg)	24/182/206
CV181040 Phase 3 N=743	SU failure subjects: 4 week lead in Gly 7.5 mg (7.5-10%)	<u>3 Groups:</u> OL Gly 7.5 mg + Saxa 2.5 or 5 mg; or OL Gly 7.5 mg + placebo + DB Gly 2.5 mg (TDD of Gly 10 mg, titratable to 15 mg)	<u>3 Groups:</u> OL Gly 7.5 mg + Saxa 2.5 or 5 mg; or OL Gly 7.5 mg + placebo + DB Gly 2.5- 7.5 mg (titratable to a maximum of 20 mg TDD)	Met 500 mg (titratable to 2500 mg)	24/52/76
CV181013 Phase 3 N=565	TZD failure subjects: Rosi 4 or 8 mg or Pio 30 or 45 mg (7-10.5%)	<u>3 Groups:</u> OL TZD + Saxa 2.5 and 5 mg or Placebo	<u>3 Groups:</u> OL TZD + Saxa 2.5 and 5 mg or Placebo	Met 500 mg (titratable to 2500 mg)	24/52/76

Table 1. Overview of Phase 2b and 3 Studies					
Study Phase Subjects Treated	Target Population/ A1c at Screening	ST Treatment Groups	LT Treatment Groups	Rescue Treatment	Duration (Weeks) ST/LT/Total
Combination Therapy (Initial or First Line Therapy)					
CV181039 Phase 3 N=1306	Treatment naïve subjects (8-12%)	<u>4 Groups:</u> Placebo + Met IR Placebo + Saxa 10 mg; Saxa 5 mg + Met IR, Saxa 10 mg + Met IR (Met titratable 500-2000 mg per protocol)	<u>4 Groups:</u> Placebo + Met IR; Placebo + Saxa 10 mg; Saxa 5 mg + Met IR; Saxa 10 mg + Met IR	Pio 15mg (titratable to 45 mg)	24/52/76
Other Studies					
CV181008 Phase 2b N=423	Treatment naïve subjects (6.8-9.7%)	<u>Main Cohort: 6 Groups:</u> Saxa 2.5, 5, 10, 20, 40 mg or placebo Protocol Amendment 4: 2 groups added: Saxa 100 mg or Placebo	NA	NA	12/NA/16 (0-40 mg Cohort) 6/NA/10 (0, 100 mg Cohort)
CV181041 Phase 3 MOA N=36	Treatment naïve subjects (6-8%)	<u>2 Groups:</u> Saxa 5 mg or Placebo	<u>2 Groups:</u> Saxa 5 mg or Met 500 mg (titrated to 1000 mg TDD per protocol)	NA	12/104/116
qam=morning dosing; qpm=evening dosing; 2.5/5 mg=titration from 2.5 to 5 mg DB=double-blind; Gly=glyburide; LT=long-term; Met=metformin; MOA=mechanism of action; NA=not applicable; OL=open-label; Pio=Pioglitazone; Rosi=Rosiglitazone; Saxa=Saxagliptin; ST=short-term; SU=sulfonylurea; TDD=total daily dose; TZD=thiazolidinedione; Wks=weeks					
Source: Applicant's Summary of Clinical Safety, Table 1.1B					

Table 2 summarizes the glycemic rescue criteria for the six Core studies. The glycemic rescue criteria differed slightly between clinical studies. For example, some studies used fasting plasma glucose measured at a central laboratory, whereas other studies used mean fasting glucose criteria based on fingerstick data collected over several days preceding the clinic visit. The glycemic rescue criteria are reasonable, although the sponsor did not explain the reason for the differing methodology between clinical studies.

Table 2. Rescue Criteria for Lack of Glycemic Control for the ST Period of the Core Phase 3 Studies						
	CV181011	CV181038	CV181013	CV181040	CV181014	CV181039
FPG>240 mg/dL (central lab)	Weeks 4,6		Weeks 4,6		Weeks 4,6	
FPG>220 mg/dL (central lab)	Week 8		Week 8		Week 8	
FPG>200 mg/dL (central lab)	Weeks 12, 16, 20, 24		Weeks 12, 16, 20, 24		Weeks 12, 16, 20, 24	
Mean FPG> 240 mg/dL Or MFWBG>221 mg/dL*		Week 6		Weeks 4,6		Week 6
Mean FPG>220 mg/dL Or MFWBG>203 mg/dL*		Week 8		Week 8		Week 8
Mean FPG>200 mg/dL Or MFWBG>185 mg/dL*		Weeks 12, 16, 20, 24		Weeks 12, 16, 20, 24		Weeks 12, 16, 20, 24
FPG=fasting plasma glucose; MFWBG=mean fasting whole blood glucose *For studies CV181038 and 181040, mean fasting glucose was calculated based on fingerstick data from self-monitored blood glucoses for at least 3 of the 5 days preceding the visit. For study CV181039, mean fasting glucose was calculated based on fingerstick data taken during the study visit and from at least 2 of the 3 days preceding the study visit.						
<i>Source: Summary of Clinical Efficacy, Table 1.5A</i>						

Some notable study design differences include the following:

- Study CV181038 was the only study that allowed for dose titration of saxagliptin. For subjects randomized to the 2.5/5 mg qam treatment group, saxagliptin was initiated at 2.5 mg and titrated to 5 mg based on criteria summarized in Table 3 below. These subjects were also eligible for a second titration to 10 mg qam at Week 24 prior to entering the LT period.

Table 3. CV181038: Saxagliptin Titration Criteria during ST Period		
Visit	Mean Fasting Plasma Glucose (MFPG)	Mean Fasting Whole Blood Glucose (MFWBG)
Week 4	≥150 mg/dL	≥140 mg/dL
Week 8	≥140 mg/dL and ≤220mg/dL	≥131 mg/dL and ≤203 mg/dL
Weeks 12 and 24	≥126mg/dL and ≤200mg/dL	≥118 mg/dL and ≤185 mg/dL
<i>Source: Applicant's Clinical Study Report, CV181038, Table 3.1.2A</i>		

- All subjects in Study CV181040 discontinued their current sulfonylurea therapy and began treatment with open-label glyburide 7.5 mg. Subjects randomized to placebo received an additional glyburide 2.5 mg. In subjects with hypoglycemia, the dose of open-label glyburide could be decreased once to 5 mg per day during the ST period at the Investigator's discretion. Blinded glyburide could have been uptitrated to 5 mg at Weeks 2 and 4 according to the criteria below.

Table 4. Titration Criteria for Subjects Assigned to Placebo Plus Upward Titrated Glyburide Treatment Group During The short-term Double-blind Treatment Period		
Visit	MFPG mg/dL	MFWBG mg/dL
Weeks 2 and 4	≥100 mg/dL	≥95 mg/dL
MFPG=mean fasting plasma glucose		
MFWBG=mean fasting whole blood glucose		

BASELINE DEMOGRAPHICS

Baseline demographics for the eight trials included in the safety database are summarized in Table 5. Generally the treatment groups were balanced for these baseline parameters so the results shown for each study are for the treatment groups combined.

All patients were 18 years or older with an average age of about 55 years for all the studies. Studies CV181038 and CV181040 had the highest proportion of patients 65 years or older (18%). About one-half of the population was male; the proportion of males ranged from 39% in Study CV181041 to 58% in Study CV181008. The majority of patients were Caucasian. The average body mass index varied from a low of 29 kg/m² in Study CV181040 to 33 kg/m² in Study CV181041.

In trials of predominantly treatment-naïve patients, the average time since diagnosis of diabetes was 2-3 years while in the add-on trials of previously-treated patients the

average time was 5-7 years. About one-half of the patients in these 8 studies had a history of hypertension while generally less than 10% had a history of coronary artery disease (CAD).

Based on medical history and lipids, no single study appears to have a population of patients at particularly high risk for cardiovascular events. The studies with the highest placebo rates of major adverse cardiovascular events (MACE) (add-on Studies CV181040 and CV181014, MACE results in Table 11) had a higher percentage of use of cardiovascular (CV) medications (~57% vs. ~45% for the monotherapy studies).

Table 5 Baseline demographics by study with treatment arms combined¹

N	Monotherapy Trials				Add-on Trials			FDC ²
	08	11	38	41	13 TZD	14 MET	40 GLY	39 MET
	338	401	365	36	565	743	768	1306
<u>Age (years)</u>								
Mean (SD)	54 (10)	53 (11)	55 (10)	56 (8)	54 (10)	55 (10)	55 (10)	52 (11)
Range	23-71	18-77	21-76	43-69	21-76	20-77	18-76	19-77
% ≥ 65 years old	14%	16%	18%	11%	15%	16%	18%	13%
<u>Gender</u>								
% males	58%	51%	46%	39%	50%	51%	45%	49%
<u>BMI (kg/m²)</u>								
Mean (SD)	31 (4)	32 (5)	31 (5)	33 (4)	30 (6)	31 (5)	29 (5)	30 (5)
% ≥ 30	~50%	62%	54%	78%	45%	57%	40%	51%
<u>Duration of Diabetes (yrs)</u>								
Mean (SD)	2 (3)	3 (3)	2 (3)	3 (4)	5 (5)	6.5 (5)	6.9 (6)	1.7 (3.1)
History of CAD	<3%	5%	13%	NA	4%	3%	3%	8%
History of hypertension	46%	48%	58%	47%	55%	59%	53%	51%
Previous diabetes treatment	15%	2.5%	5%	0%	100%	100%	100%	2%
Used Baseline CV medication?	NA	45%	NA	44%	53%	58%	55%	48%
<u>HbA1c (%)</u>								
Mean (SD)	7.9 (1.0)	7.9 (1.0)	7.9 (0.9)	6.8 (0.6)	8.3 (1.0)	8 (0.9)	8.4 (0.9)	9.5 (1.3)
% < 8%	~55%	60%	55%	~99%	45%	51%	33%	10%
<u>HDL-cholesterol (mg/dL)</u>								
Mean (SD)	44 (10)	46 (10)	45 (9)	NA	46 (10)	47 (10)	44 (11)	44 (12)
<u>LDL-cholesterol (mg/dL)</u>								
Mean (SD)	117 (32)	115 (40)	122 (35)	NA	114 (36)	100 (32)	113 (34)	125 (36)

¹ The numbers in this table were extracted from the individual study reports provided by the applicant. NA indicates that the value was not reported in the NDA study report. SD=standard deviation; CAD=coronary artery disease; CV=cardiovascular

² FDC=Fixed dose combination trial

PATIENT DISPOSITION AND GLYCEMIC RESCUE

In this section, the patient disposition for the short-term periods of the Core Phase 3 studies is summarized in tabular format (Table 6) and graphically (Figure 2 on the following page). Total exposure in the short-term and long-term periods is summarized in the following section. Of particular interest in these trials is the incidence of glycemic rescue because patients requiring glycemic rescue continued to be followed into the long-term period and are therefore included in the safety database for the short-term plus long-term periods. These rescued patients continued on blinded, randomized treatment and on open-label rescue medication to lower HbA1c.

Across all Core Phase 3 studies, about 74% of subjects completed the ST period with the lowest completion rates generally seen for the placebo groups. The highest completion rate was seen in Study CV181013 (~80%) and the lowest in Study CV181011 (~65%). In all studies, the completion rate for U.S. sites (nearly 1/3 of the overall population) was about 20% lower than for the sites from other countries; this difference was due to a difference in glycemic rescue rates, although the same rescue criteria were supposed to be applied across all countries.

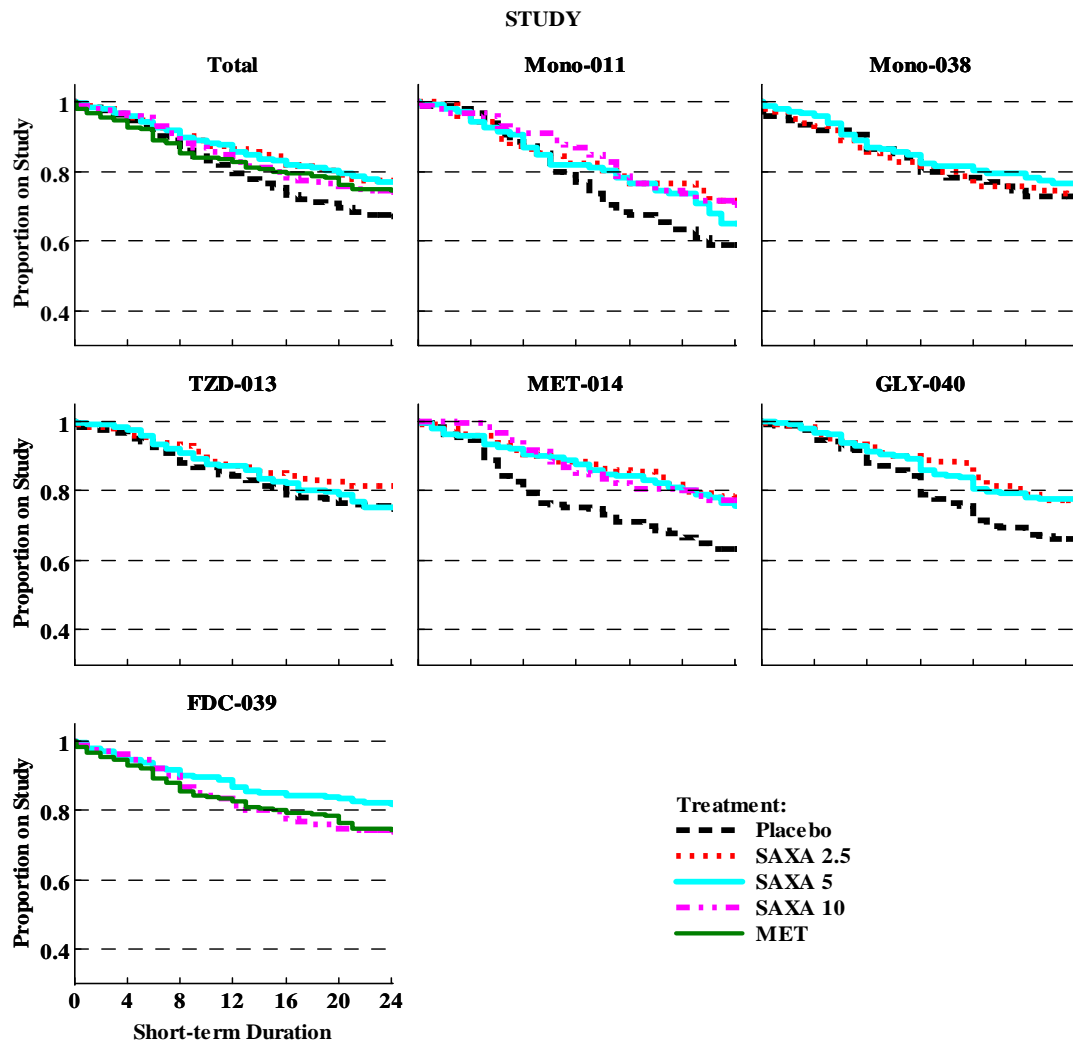
Study	Treatment Group	No. Randomized and Treated	Completed n (%)	Discontinued for lack of efficacy (excluding rescue) n (%)	Rescued n (%)
CV181011	Saxa 2.5 mg	102	73 (72%)	9 (9%)	14 (14%)
	Saxa 5 mg	106	68 (64%)	8 (8%)	21 (20%)
	Saxa 10 mg	98	69 (70%)	9 (9%)	14 (14%)
	Placebo	95	55 (58%)	15 (16%)	25 (26%)
	Open Label	66	25 (38%)	n/a	n/a
CV181038	Saxa 2.5 mg	74	55 (74%)	1 (1%)	8 (11%)
	Saxa 5 mg	74	57 (77%)	0 (0)	10 (14%)
	Saxa 2.5/5 mg	71	52 (73%)	1 (1%)	9 (13%)
	Saxa 5 mg qpm	72	55 (76%)	0 (0)	8 (11%)
	Placebo	74	53 (72%)	1 (1%)	11 (15%)
CV181013	Saxa 2.5 mg + TZD	195	159 (82%)	1 (1%)	18 (9%)
	Saxa 5 mg + TZD	186	140 (75%)	0 (0)	12 (7%)
	Placebo + TZD	184	138 (75%)	5 (3%)	14 (8%)
CV181040	Saxa 2.5 mg + Gly	248	192 (77%)	3 (1%)	42 (17%)
	Saxa 5 mg + Gly	253	195 (77%)	1 (0.4%)	41 (16%)
	Placebo + Gly	267	176 (66%)	1 (0.4%)	78 (29%)
CV181014	Saxa 2.5 mg + Met	192	148 (77%)	9 (5%)	25 (13%)
	Saxa 5 mg + Met	191	143 (75%)	12 (6%)	22 (12%)
	Saxa 10 mg + Met	181	140 (77%)	11 (6%)	25 (14%)
	Placebo + Met	179	112 (63%)	20 (11%)	42 (25%)
CV181039	Saxa 5 mg + Met	320	262 (82%)	1 (0.3%)	23 (7%)
	Saxa 10 mg + Met	323	261 (81%)	0 (0)	18 (6%)
	Saxa 10 mg	335	225 (67%)	2 (1%)	69 (21%)
	Metformin	328	243 (74%)	6 (2%)	27 (8%)

Source: Applicant's Summary of Clinical Efficacy, Table 3.1.2B

The primary reason for discontinuation from the short-term period in all groups was lack of efficacy leading to glycemic rescue with add-on therapy. As expected, subjects in the placebo groups generally had the highest rates of glycemic rescue. One exception is Study CV181039 (initial combination therapy with metformin), where the saxagliptin 10 mg group had markedly high rates of glycemic rescue (21%) compared with the groups that received saxagliptin + metformin or those that received metformin alone. A graph showing the rates of rescue is provided in Appendix 2.

Generally less than 4% of patients in each treatment group dropped out due to adverse events with no clear dose response.

Figure 2 Proportion of patients on study during the short-term period of 24 weeks by study and by treatment group (note that the y-axis starts at 0.3)



EXPOSURE

Short-term plus long-term exposure is summarized below for the original NDA submission (Table 7) and for the updates from the 120-Day Safety Update (Table 8, note that the updated database is the primary database for the MACE analyses). From the original NDA submission, 2642 subjects were exposed to saxagliptin for ≥ 24 weeks, and 1080 subjects were exposed to saxagliptin for ≥ 52 weeks. With the information provided in the 120-day Safety Update, the number of subjects exposed to saxagliptin ≥ 52 weeks nearly doubled from 1080 patients in the original NDA to 1937 in the update. Including data from the 120-day Safety Update, saxagliptin-treated subjects were exposed to study drug for a median of 62 weeks and the comparator for a median of 60 weeks.

The applicant's original analysis of MACE that is discussed later in this review, was based on the exposure shown in Table 7. FDA analyses and other analyses performed by the applicant were based on the exposure shown in Table 8.

Table 7 Exposure in ST + LT Periods from the NDA submission: Phase 2/3 Studies

	Saxa 2.5mg	Saxa 5mg	Saxa 10mg	Saxa 20mg	Saxa 40mg	Saxa 100mg	All Saxa ^a	Placebo	Met
	N=937	N=1269	N=1066	N=54	N=52	N=44	N=3422	N=923	N=328
N (%) ≥ 24	773 (83%)	1038 (82%)	831 (78%)	0	0	0	2642 (77%)	679 (74%)	263 (80%)
N (%) ≥ 52	417 (45%)	399 (31%)	264 (25%)	0	0	0	1080 (32%)	352 (38%)	8 (2%)
Mean (SD)	52.1 (28)	46.6 (27)	44.6 (31)	11.2 (2.6)	11.6 (2.4)	6.1 (0.4)	45.9 (29)	46.3 (29)	31.3 (14)
Median	50.1	38.1	37	12.1	12.1	6.1	37.6	48.7	33.9
Range	0.1, 116.9	0.1, 119.0	0.1, 117.1	3.9, 16.0	1.3, 14.6	5.1, 8.1	0.1, 119.0	0.1, 116.1	0.1, 75.4

Adapted from Applicant's "Response to 74 Day Letter"

^aIncluded saxagliptin 20mg (N=54), saxagliptin 40mg (N=52), saxagliptin 100mg (N=44) in Study CV181008 and saxagliptin 10mg open-label group in Study CV181011

Table 8 Exposure in ST + LT Periods from the 120-Day Safety Update: Phase 2/3 Studies

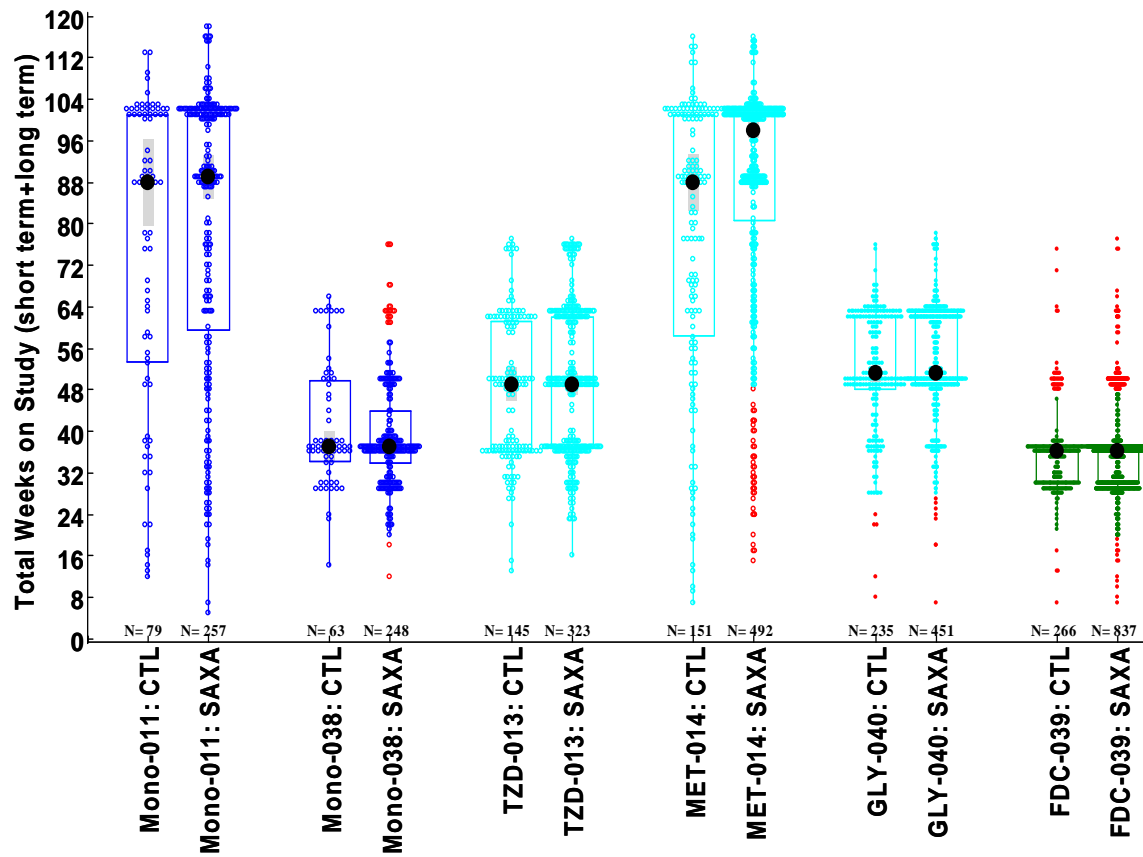
Weeks	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1066	All Saxa N=3422	Control N=1251
N (%) ≥ 24	773 (83%)	1046 (82%)	836 (78%)	2655 (78%)	945 (76%)
N (%) ≥ 52	622 (66%)	772 (61%)	543 (51%)	1937 (57%)	689 (55%)
Mean (SD)	64.0 (35)	60.1 (33)	58.5 (36)	58.5 (36)	53.9 (33)
Median	65.1	63	52.6	62.3	60
Range	0.1, 141.6	0.1, 144.3	0.1, 157.1	0.1, 157.1	0.1, 141.1

Source: Applicant's 120-day Safety Update, Appendix 1.4.5

The figure below illustrates the total exposure in weeks for the combined short-term and long-term segments of the Phase 3 core trials by study and treatment groups. Each symbol on the boxplots represents a single patient with the large black symbol

representing the median and red symbols representing outliers. With the exception of Study CV181014 (treatment difference of about 10 weeks), the exposure in the treatment groups is comparable. There is variability across the studies with notably higher exposure seen for patients in Studies CV181011 and CV181014. The placebo MACE event rate for Study CV181014 was one of the two highest MACE event rates (2.2%, Table 11) but was equivalent to the MACE event rate seen for Study CV181040 with much lower exposure.

Figure 3 Patient exposure (weeks) by study and treatment group (all saxagliptin arms and control) for short-term (ST) and long-term (LT) study periods



Major Adverse Cardiovascular Events

Background

In July 2008, the Endocrine and Metabolic Drugs Advisory Committee voted in favor of requiring applicants to conduct long-term clinical trials or to provide equivalent evidence in ruling out an unacceptable cardiovascular safety risk. Following that meeting, the FDA issued a Guidance entitled “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes”. This Guidance (which is included in the FDA briefing document) makes recommendations for changes in the clinical development program for drugs and biologics under development for the treatment of type 2 diabetes in order to evaluate the cardiovascular safety of the investigational therapy.

The Guidance conveys the following important points:

- An independent cardiovascular endpoints committee should be established 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 possible other endpoints.
- Phase 2 and phase 3 clinical trials should be appropriately designed and conducted so that a meta-analysis can be performed at the time of data analysis. This includes enrolling subjects with a higher risk of cardiovascular events.
- It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain sufficient numbers of events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these drugs that are used as chronic therapies.
- For completed studies, a comparison of the incidence of important cardiovascular events occurring with the study drug versus the control group should be performed. Sponsors should show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be done by several methods: the meta-analysis of the phase 2 and phase 3 clinical trials or an additional single, large safety trial should be conducted before NDA/BLA submission.
- If the upper bound of the two-sided 95 percent confidence interval is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be done by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This trial would be a required postmarketing safety trial.
- If the premarketing application contains data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk is less than 1.3, a postmarketing cardiovascular trial may not be necessary.

The relevance of this Guidance to drugs that are currently in development is clear. However, the New Drug Application for saxagliptin was under review within the Division at the time the Guidance was issued. The role of the applicability of the Guidance to this drug is less clear, particularly because the clinical development program was not prospectively designed as outlined by the Guidance. Nevertheless, it is vital that the cardiovascular risk of saxagliptin be assessed prior to approval. The remainder of this document describes FDA's method of making this assessment.

Definitions of Major Adverse Cardiovascular Events (MACE)

During the initial review of this NDA and another NDA that is the subject of the April 2, 2009 advisory committee meeting, requests for MACE analyses were sent to the respective applicants. While results of these analyses were somewhat informative, it was noticed that the individual terms chosen to represent "MACE" differed widely between the two sponsors. The Division determined that more uniform MACE analyses were imperative to evaluating cardiovascular risk for these anti-diabetic products.

Post hoc adjudication of all events was not possible due to inadequate information. Therefore, it was decided to instead use a collection of MedDRA preferred terms for myocardial infarction and stroke, as originally coded, with the addition of cardiovascular deaths. Two endpoints were chosen, one intended to broadly capture all possible strokes and myocardial infarctions; and one intended to include those terms which seemed likely to be chosen as the term to describe an event that truly was a myocardial infarction or a stroke. The broad endpoint was a composite endpoint of cardiovascular death, and all preferred terms in the Standardized MedDRA Queries (SMQ) for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents." This endpoint is referred to as the "Broad SMQ MACE". The more specific endpoint, referred to as the "Custom MACE", is a subset of the "Broad SMQ MACE". This endpoint was developed by collaboration of three FDA clinical reviewers. Without considering which events had actually occurred, each clinical reviewer independently reviewed the list of all possible terms included in the "Broad SMQ MACE". The clinical reviewer then considered each term, with this question in mind: "If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?", with the goal of selecting only those Preferred Terms that seemed highly likely to represent events that would truly be a myocardial infarction or a stroke. The interest was also that these events likely represent acute events with a mechanism of atherosclerotic plaque development followed by plaque rupture/thrombosis (as opposed to events with non-atherosclerotic mechanisms, e.g. rupture of congenital aneurysm). The three reviewers' lists were compared, and any terms for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached on which terms were included. The clinical reviewer acknowledges that this is an imperfect process; other reasonable physicians may have chosen a different set of terms. Also, although the MedDRA SMQs are broad, they may not be all-inclusive. For example, the MedDRA Broad Myocardial Infarction SMQ does not contain the terms "cardiac arrest" or "circulatory collapse".

A comprehensive list of preferred terms that defined the two individual endpoints described above is organized alphabetically in Table 9. In addition, Table 9 includes the preferred terms used in the initial MACE analysis conducted by the applicant (“Prior BMS MACE”) submitted prior to FDA’s Information Request for the uniform MACE analyses.

The saxagliptin database was queried for these terms with the first event for each patient counted as a MACE event. Only these first events were analyzed by both the applicant and by FDA.

Table 9 Listing of preferred terms queried for MACE analyses			
	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Myocardial Infarction Terms			
Acute coronary syndrome	X		X
Acute myocardial infarction	X	X	X
Agonal rhythm			X
Blood creatine phosphokinase abnormal	X		
Blood creatine phosphokinase increased	X		
Blood creatine phosphokinase MB abnormal	X		
Blood creatine phosphokinase MB increased	X		
Cardiac arrest			X
Cardiac death			X
Cardiac enzymes increased	X		
Cardio-respiratory arrest			X
Coronary artery embolism	X		X
Coronary artery occlusion	X		
Coronary artery reocclusion	X		
Coronary artery thrombosis	X	X	X
Coronary bypass thrombosis	X		X
Electrocardiogram Q wave abnormal	X		
Electrocardiogram ST segment abnormal	X		
Electrocardiogram ST segment elevation	X		
Electrocardiogram ST-T segment elevation	X		
Electromechanical dissociation			X
Infarction	X		
Myocardial infarction	X	X	X
Myocardial reperfusion injury	X		X
Papillary muscle infarction	X	X	X
Postinfarction angina	X		
Postprocedural myocardial infarction	X	X	X
Scan myocardial perfusion abnormal	X		
Silent myocardial infarction	X	X	
Sudden cardiac death			X
Sudden death			X
Troponin I increased	X		
Troponin increased	X		
Troponin T increased	X		
Vascular graft occlusion	X		
Ventricular asystole			X
Stroke Terms			
Agnosia	X		

Table 9 Listing of preferred terms queried for MACE analyses			
	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Amaurosis fugax	X		
Angiogram cerebral abnormal	X		
Aphasia	X		
Balint's syndrome	X		
Basal ganglia hemorrhage	X		X
Basilar artery occlusion	X		
Basilar artery stenosis	X		
Basilar artery thrombosis	X	X	X
Brain stem hemorrhage	X		X
Brain stem infarction	X	X	X
Brain stem ischemia	X		
Brain stem stroke	X	X	
Brain stem thrombosis	X	X	X
Capsular warning syndrome	X		
Carotid aneurysm rupture	X		
Carotid arterial embolus	X	X	X
Carotid arteriosclerosis	X		
Carotid artery aneurysm	X		
Carotid artery bypass	X		
Carotid artery disease	X		
Carotid artery dissection	X		
Carotid artery insufficiency	X		
Carotid artery occlusion	X		
Carotid artery stenosis	X		
Carotid artery stent insertion	X		
Carotid artery thrombosis	X	X	X
Carotid endarterectomy	X		
Central pain syndrome	X		
Cerebellar artery occlusion	X		
Cerebellar artery thrombosis	X		X
Cerebellar embolism	X		X
Cerebellar hemorrhage	X		X
Cerebellar hematoma	X		
Cerebellar infarction	X	X	X
Cerebellar ischemia	X		
Cerebral aneurysm ruptured syphilitic	X		
Cerebral arteriosclerosis	X		
Cerebral arteriovenous malformation hemorrhagic	X		
Cerebral artery embolism	X	X	X
Cerebral artery occlusion	X		
Cerebral artery stenosis	X		
Cerebral artery thrombosis	X	X	X
Cerebral hematoma	X		
Cerebral hemorrhage	X		X
Cerebral hemorrhage fetal	X		
Cerebral hemorrhage neonatal	X		
Cerebral infarction	X	X	X
Cerebral infarction fetal	X		
Cerebral ischemia	X		

Table 9 Listing of preferred terms queried for MACE analyses			
	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Cerebral thrombosis	X	X	X
Cerebral vasoconstriction	X		
Cerebral venous thrombosis	X		
Cerebrovascular accident	X	X	X
Cerebrovascular accident prophylaxis	X		
Cerebrovascular disorder	X		
Cerebrovascular insufficiency	X		
Cerebrovascular spasm	X		
Cerebrovascular stenosis	X		
Charcot-Bouchard microaneurysms	X		
Diplegia	X		
Dysarthria	X		
Embolic cerebral infarction	X	X	X
Embolic stroke	X	X	X
Hematomyelia	X		
Hemiparesis	X		
Hemiplegia	X		
Hemorrhage intracranial	X		
Hemorrhagic cerebral infarction	X	X	X
Hemorrhagic stroke	X	X	X
Hemorrhagic transformation stroke	X	X	X
Intracerebral aneurysm operation	X		
Intracerebral hematoma evacuation	X		
Intracranial aneurysm	X		
Intracranial hematoma	X		
Intraventricular hemorrhage	X		X
Intraventricular hemorrhage neonatal	X		
Ischemic cerebral infarction	X	X	X
Ischemic stroke	X	X	X
Lacunar infarction	X	X	X
Lateral medullary syndrome	X	X	X
Meningorrhagia	X		
Millard-Gubler syndrome	X		
Monoparesis	X		
Monoplegia	X		
Moyamoya disease	X	X	
Paralysis	X		
Paralysis flaccid	X		
Paraparesis	X		
Paraplegia	X		
Paresis	X		
Postprocedural stroke	X	X	X
Precerebral artery occlusion	X		X
Putamen hemorrhage	X		X
Quadriparesis	X		
Quadriplegia	X		
Red blood cells CSF positive	X		
Reversible ischemic neurologic deficit	X		
Ruptured cerebral aneurysm	X		
Spastic paralysis	X		

Table 9 Listing of preferred terms queried for MACE analyses			
	FDA Broad SMQ MACE	FDA Custom MACE	Prior BMS MACE
Spastic paraplegia	X		
Spinal artery embolism	X		
Spinal cord hemorrhage	X		
Spinal hematoma	X		
Stroke in evolution	X	X	X
Subarachnoid hemorrhage	X		
Subdural hemorrhage	X		
Subdural hemorrhage neonatal	X		
Thalamic infarction	X	X	X
Thalamus hemorrhage	X		X
Thromboembolic stroke			X
Thrombotic cerebral infarction	X	X	X
Thrombotic stroke	X	X	X
Transient ischemic attack	X		
Vascular encephalopathy	X		
Vertebral artery occlusion	X		
Vertebral artery stenosis	X		
Vertebral artery thrombosis	X		X
Vertebrobasilar insufficiency	X		
Visual midline shift syndrome	X		
Wallenberg syndrome	X	X	X

In addition to events identified through MedDRA preferred terms, all data for subjects who died were assessed retrospectively to ascertain if the underlying cause was CV-related based on the descriptive preferred term and a review of case details. Deaths were classified as CV-related if the associated preferred terms either: 1) fell under the System-Organ-Class of Cardiac Disorders; 2) were stroke-related; 3) were suggestive of sudden death; or 4) were related to other vascular events. This approach yielded six such CV deaths among saxagliptin-treated patients; four of these occurred in the ST+LT period as reported in the NDA submission. The two additional CV deaths, determined by a clinical review of all deaths, occurred between the NDA submission and the 120-Day Safety Update cutoff dates. These two deaths were not initially identified as MACE events because of ambiguity related to their last dose of study drug at the time of the interim database lock. It was later confirmed that both subjects were taking study drug until the fatal event.

One subject in the placebo group of Study CV181038 had an “extensive anterior wall ST elevation myocardial infarction” that was not reported as a MACE event before database lock. This subject was not included in the FDA MACE analyses. Note that inclusion of this one event would weigh in favor of saxagliptin but the impact would be trivial given the small sample size and the low event rates of the study. Note that the applicant has included this event in some analyses.

Analysis Populations

As already described, the database for the analysis of MACE is composed of 8 Phase 2b/3 studies; Studies CV181008, CV181011, CV181013, CV181014, CV181038, CV181039, CV181040, and CV181041. Seven of these eight studies are placebo-controlled and one is metformin-controlled (Study CV181039).

Analyses were performed of the following:

1. short-term (ST), 24-week periods
2. short-term (ST) plus long-term (LT) periods (120-day Safety Update database).

The ST data excludes data collected after glycemic rescue; while the ST + LT data includes data following initiation of rescue therapy. All patients (rescued patients and trial completers) who continued into the long-term period remained on double-blind, randomized treatment. In the monotherapy trials (CV181011 and CV181018), placebo-treated patients who completed the ST period without being rescued, were given double-blind metformin in addition to placebo during the LT period. The majority of randomized patients continued into the long-term period of the study; 78% of saxagliptin-treated patients and 76% of comparator-treated patients. In the long-term period, rescued patients were also being treated with open-label rescue anti-diabetic medication. It is reasonable to assess safety from the ST+LT data because blinded treatment is continued. One must assume however that the add-on open-label rescue medication will not differentially impact the collection of safety data. The latter may be problematic given that the use of rescue was significantly different between saxagliptin and comparator. Nonetheless, there is value in the LT safety evaluation because it compares saxagliptin to a background of standard anti-diabetic therapies, while attempting to maintain some degree of balance in glycemic control between treatment groups. Looking then at both ST data and ST+LT data is informative.

The median exposure for the two populations studied were:

ST period	SAXA: 24 weeks	Comparator: 24 weeks
ST+LT periods	SAXA: 62 weeks	Comparator: 60 weeks

Statistical Methods

With the exception of Study CV181041, all studies included multiple doses of saxagliptin with most studies including doses of 2.5 mg, 5 mg and 10 mg. The applicant's proposed dose for marketing is 5 mg. For the MACE analyses, the events by dose were examined to determine if there was any evidence of dose response (see Tables 11 and 15). Given no significant evidence of dose response, the saxagliptin arms were combined for comparison to the control. For all MACE analyses (applicant's and FDA's), the first MACE event is analyzed. Few patients had multiple MACE events so an analysis of multiple events did not seem warranted.

The primary FDA analysis of MACE was an exact test of 2x2 contingency tables stratified on study (using StatXact via Proc Stratify in SAS). This test is performed by considering all possible re-arrangements of treatment assignment labels applied to the observed data and calculating the corresponding test statistics. The exact p-value is the tail probability of results more extreme than the observed result. Heterogeneity among studies was ascertained by Zelen's exact test; these results uniformly showed no evidence of significant heterogeneity and are not reported here. The odds ratios are conditional maximum likelihood estimates where a value greater than 1 indicates greater risk due to saxagliptin. The confidence intervals shown are exact 95% confidence intervals (CI). Because this statistical method excludes studies with no events, 3 studies with about 20% of the patients were excluded from the analysis of the Custom MACE endpoint; no studies are excluded for the Broad SMQ MACE endpoint.

Because all studies are included in the computation of the risk difference, a common risk difference was computed by FDA using a fixed effects model (Mantel-Haenszel method).

The estimates of incidence rate ratios (events per person-years) and 95% CIs shown in the table of results for both MACE endpoints were computed by the applicant using an exact procedure based on a poisson model stratifying on study. These results provide estimates adjusted for exposure.

Forest plots of Custom and Broad SMQ MACE for the short-term plus long-term periods visually depict the odds ratios (OR) and confidence intervals for individual studies. In these plots, the symbol for the OR is sized by the inverse variance (studies with more precise results are given more weight in the computation of the common odds ratio and a symbol proportional to the weight). A log scale is used for the x-axis and a reference line is shown at 1. The ORs depicted in the graphs are computed using the stratified Mantel-Haenszel test with continuity correction (R software was used to compute and graph the ORs and confidence intervals). For this statistical method, 0.5 is added to all 4 cells for trials with 0 events in one or both treatment groups to compute an OR and to include the study in the graph. For both endpoints, the Mantel-Haenszel estimate was close to the conditional maximum likelihood estimate shown in the tables.

To depict the timing of events in the two treatment groups, Kaplan-Meier curves are shown. In addition, Kaplan-Meier curves for each study were created (not shown here) to

determine if the individual study results were consistent with the overall results; this was generally the case and therefore pooling of the data for descriptive purposes was considered acceptable.

Results of MACE Analyses

The results of FDA analyses of Custom MACE and SMQ MACE are presented in the next two sections of this document. These sections then are followed by a brief discussion of analyses performed by Bristol-Myers Squibb (BMS), the applicant.

Results for Custom Mace

All events that satisfied the definition of a Custom MACE event are shown in Table 10 on the following page; the top part of the table shows the ST period events and the bottom, the ST+LT events. The number of events for each preferred term (PT) is the number of first events for that particular PT so patients are counted once on each line of the table.

Looking at the individual PTs, there is no evidence of dose response and no single PT is dominant.

Table 10 Custom MACE: Observed Preferred Terms

ST Treatment Period					
System-Organ-Class (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Comparator
Preferred Term (%)	N=937	N=1269	N=1000	N=3356	N=1251
Total Subjects with an Event	1 (0.1)	1 (<0.1)	2 (0.2)	4 (0.1)	7 (0.6)
Cardiac Disorders	0	0	1 (0.1)	1 (<0.1)	5 (0.4)
Acute Myocardial Infarction	0	0	0	0	1 (<0.1)
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiogenic Shock	0	0	0	0	1 (<0.1)
Myocardial Infarction	0	0	1 (0.1)	1 (<0.1)	3 (0.2)
General Disorders and Administration Site Conditions	0	0	0	0	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Nervous System Disorders	1 (0.1)	1 (<0.1)	1 (0.1)	3 (<0.1)	1 (<0.1)
Cerebrovascular Accident	1 (0.1)	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009, Table 2.2

ST + LT Treatment Period					
System Organ Class (%)	Saxa 2.5mg	Saxa 5mg	Saxa 10mg	All Saxa	Comparator
Preferred Term (%)	N=937	N=1269	N=1000	N=3356	N=1251
Total Subjects with an Event	6 (0.6)	6 (0.5)	11 (1.1)	23 (0.7)	17 (1.4)
Cardiac Disorders	2 (0.2)	4 (0.3)	4 (0.4)	10 (0.3)	12 (1.0)
Acute Myocardial Infarction	2 (0.2)	3 (0.2)	0	5 (0.1)	5 (0.4)
Atrioventricular Block Complete	0	1 (<0.1)	0	1 (<0.1)	0
Cardiogenic Shock	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Myocardial Infarction	0	1 (<0.1)	2 (0.2)	3 (<0.1)	5 (0.4)
Arteriosclerosis Coronary Artery	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Arrest	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiac Failure Congestive	0	0	0	0	1 (<0.1)
General Disorders and Administration Site Conditions	0	1 (<0.1)	1 (0.1)	2 (<0.1)	2 (0.2)
Sudden Death	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Nervous System Disorders	4 (0.4)	3 (0.2)	5 (0.5)	12 (0.4)	3 (0.2)
Cerebrovascular Accident	3 (0.3)	2 (0.2)	3 (0.3)	8 (0.2)	2 (0.2)
Cerebral Infarction	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Ischemic Stroke	0	0	1(0.1)	1 (<0.1)	0

Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.4

Event rates of Custom MACE were low across all groups (Tables 10 and Table 11 top) and there is no evidence of a dose response in individual studies or for the studies pooled. Overall, the rate in the comparator group (0.6%) exceeded that of all saxagliptin-treated subjects (0.1%). In particular, cardiac disorders (Table 10) were seen more frequently in the comparator group (0.4%) compared to the saxagliptin groups (<0.1%). The rates of events in nervous system disorders were comparable for all groups.

This changed only slightly when looking at Custom MACE for the ST and LT treatment periods (Table 11 bottom). Using both periods, the comparator rate (1.4%) still exceeded that of all saxagliptin groups (0.7%), although was less marked than using events from the ST alone. Once again, cardiac disorders (Table 10) were seen more frequently in the comparator group (1.0% versus 0.3% for saxagliptin-treated subjects). Also, similar to the analysis of the ST period, nervous system disorders appeared comparable across all groups.

Table 11 Incidence of Custom MACE by Dose of Saxagliptin and by Study

ST Treatment Period					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	1/937 (0.1)	1/1269 (<0.1)	2/1000 (0.2)	4/3356 (0.1)	7/1251 (0.6)
CV181008	0/55 (0)	0/47 (0)	0/63 (0)	0/315 (0)	0/108 (0)
CV181011	0/102 (0)	1/106 (0.9)	0/98 (0)	1/306 (0.3)	0/95 (0)
CV181013	1/195 (0.5)	0/186 (0)	NA	1/381 (0.3)	0/184 (0)
CV181014	0/192 (0)	0/191 (0)	0/181 (0)	0/564 (0)	2/179 (1.1)
CV181038	0/145 (0)	0/146 (0)	NA	0/291 (0)	0/74 (0)
CV181039	NA	0/320 (0)	2/658 (0.3)	2/978 (0.2)	3/328 (0.9)
CV181040	0/248 (0)	0/253 (0)	NA	0/501 (0)	2/267 (0.7)
CV181041	NA	0/20 (0)	NA	0/20 (0)	0/16 (0)
ST+LT Treatment Period					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	6/937 (0.6)	6/1269 (0.5)	11/1000 (1.1)	23/3356 (0.7)	17/1251 (1.4)
CV181008	0/55 (0)	0/47 (0)	0/63 (0)	0/315 (0)	0/108 (0)
CV181011	0/102 (0)	2/106 (1.9)	0/98 (0)	2/306 (0.7)	1 (1.1)
CV181013	3/195 (1.5)	1/186 (0.5)	NA	4/381 (1.0)	1/184 (0.5)
CV181014	1/192 (0.5)	1/191 (0.5)	4/181 (2.2)	6/564 (1.1)	4/179 (2.2)
CV181038	0/145 (0)	0/146 (0)	NA	0/291 (0)	0/74 (0)
CV181039	NA	1/320 (0.3)	7/658 (1.1)	8/978 (0.8)	5/328 (1.5)
CV181040	2/248 (0.8)	1/253 (0.4)	NA	3/501 (0.6)	6/267 (2.2)
CV181041	NA	0/20 (0)	NA	0/20 (0)	0/16 (0)

The lack of a dose response suggests that the saxagliptin doses may be combined for an overall analysis stratified on study.

The Custom MACE results (Table 12) show reduced risk of a CV event due to saxagliptin compared to control (predominantly placebo) with some analyses (incidence rate ratio and odds ratio for the ST period) showing statistically significant reductions of more than 50%. However, the event rates are low with a total of 11 events in the ST period and a total of 40 events in the ST+LT period and the risk difference is small (<1%) and is not statistically significant.

The results for Custom MACE do not change with analysis population (ST versus ST+LT) or with statistical method; in all cases the upper bound of the 95% confidence interval is less than 1.3. According to the guidance, meeting a boundary of 1.3 may suggest that a post-marketing study for assessing CV safety is not necessary.

Table 12 Overall Results for Custom MACE

	Saxagliptin (N=3356)	Comparator (N=1251)
Patient-years		
ST	1295	458
ST+LT	3753	1289
Events (%)		
ST	4 (0.1%)	7 (0.6%)
ST+LT	23 (0.7%)	17 (1.3%)
Events/1000 patient-years		
ST	3	15
ST+LT	6	13
Study-stratified Estimate of Treatment Difference¹ (95% CI)		
Odds Ratio – Exact method		
ST	0.21 (0.04, 0.8)	
ST+LT	0.52 (0.26, 1.04)	
Incidence Rate Ratio		
ST	0.20 (0.04, 0.79)	
ST+LT	0.48 (0.24, 0.96)	
Risk Difference		
ST	-0.4% (-1.0%, +0.1%)	
ST+LT	-0.6% (-1.3%, +0.1%)	

1- Odds ratios under 1 and risk differences less than 0 favor saxagliptin.

A forest plot (Figure 4 on the following page) of the results by study and overall for the ST+LT period show consistently favorable results for saxagliptin (with the exception of Study CV181013). Also the Kaplan-Meier curve (Figure 5 on the following page) illustrates that the event rate differences persist through the LT period.

Figure 4 Forest Plot of Custom MACE Results – ST+LT

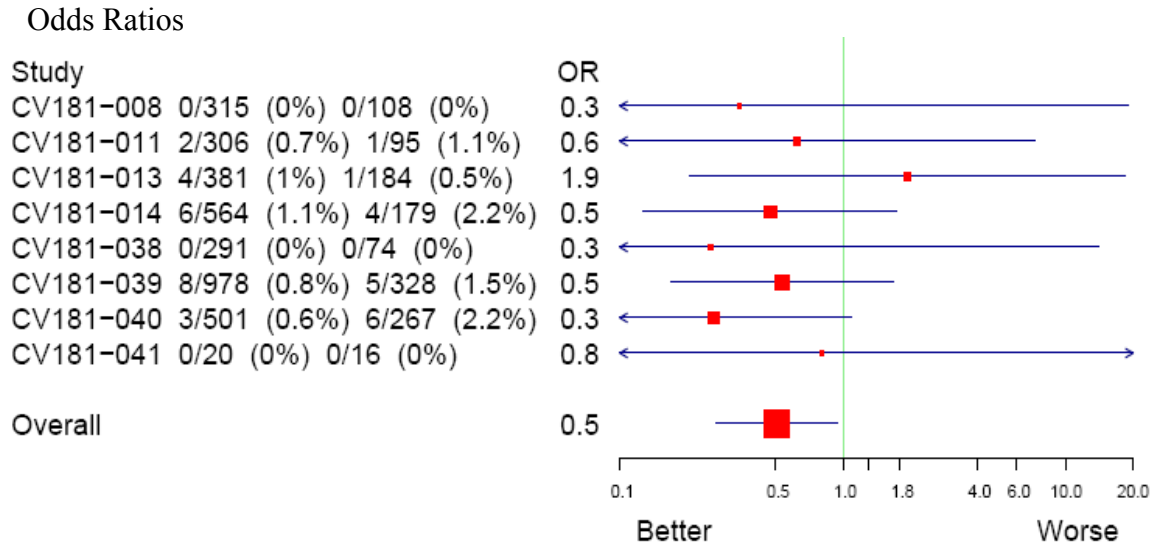
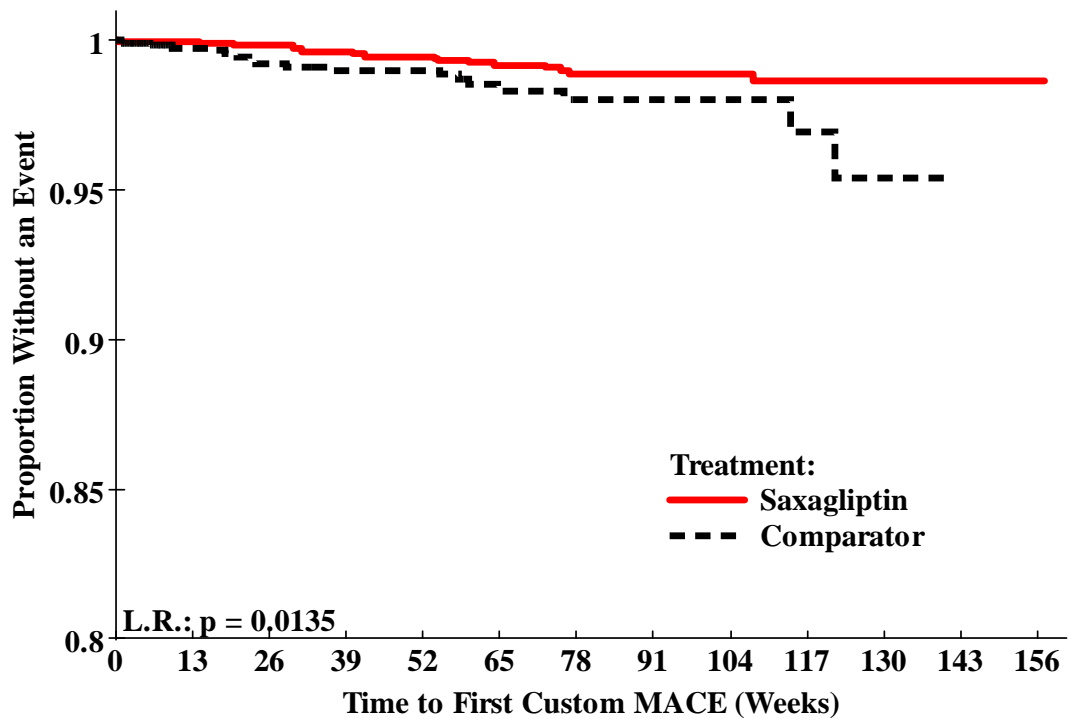


Figure 5 Kaplan-Meier Plot of Custom MACE Results – ST+LT



Results for Broad SMQ MACE

As shown earlier, the SMQ MACE endpoint is a broad endpoint so the event rate for SMQ MACE is notably greater than the rate observed for Custom MACE. In comparing SMQ MACE events from the ST period (Table 13) to Custom MACE events (Table 10), it is important to note that a disproportionately large number of subjects represented in the SMQ MACE analysis had a PT of “blood creatine phosphokinase increased”. Fifty of the 58 first SMQ MACE events for the saxagliptin group and 14 of the 25 SMQ MACE events for the comparator group were creatine phosphokinase (CPK) increases. Therefore this PT alone, which may easily not represent an important cardiovascular event, comprised a significant number of events in the broad SMQ analysis. This was also true for the ST+LT period where additional events of increased CPK were observed (Table 14); again the majority of first Broad SMQ MACE events for the saxagliptin group and about half of the events for comparator were recorded as increased CPK.

Table 13 SMQ MACE: Observed Preferred Terms

ST Treatment Period					
System Organ Class (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Comparator
Preferred Term (%)	N=937	N=1269	N=1000	N=3356	N=1251
Total Subjects with an Event	16 (1.7)	18 (1.4)	19 (1.9)	58 (1.7)	25 (2.0)
Cardiac Disorders	0	0	1 (0.1)	1 (<0.1)	5 (0.4)
Acute Myocardial Infarction	0	0	0	0	1 (<0.1)
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiogenic Shock	0	0	0	0	1 (<0.1)
Myocardial Infarction	0	0	1 (0.1)	1 (<0.1)	3 (0.2)
General Disorders and Administration Site Conditions	0	0	0	0	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Investigations	14 (1.5)	17 (1.3)	16 (1.6)	52 (1.5)	14 (1.1)
Blood Creatine Phosphokinase Increased	14 (1.5)	16 (1.3)	15 (1.5)	50 (1.5)	14 (1.1)
Electrocardiogram ST Segment Abnormal	0	1 (<0.1)	0	1 (0.1)	0
Blood Creatine Phosphokinase MB Increased	0	0	1 (0.1)	1 (0.1)	0
Nervous System Disorders	1 (0.1)	1 (<0.1)	2 (0.2)	4 (0.1)	5 (0.4)
Cerebrovascular Accident	1 (0.1)	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Carotid Artery Stenosis	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Cerebrovascular Disorder	0	0	0	0	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	0
Transient Ischemic Attack	1 (0.1)	0	0	1 (<0.1)	3 (0.2)
Vascular Disorders	1 (0.1)	0	1 (0.1)	2 (<0.1)	0
Infarction	1 (0.1)	0	1 (0.1)	2 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.1

Table 14 Preferred Terms Observed for SMQ MACE continued

ST + LT Treatment Period					
SOC (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Comparator
PT (%)	N=937	N=1269	N=1000	N=3356	N=1251
Total Subjects with an Event	28 (3.0)	37 (2.9)	30 (3.0)	100 (3.0)	41 (3.3)
Cardiac Disorders	2 (0.2)	4 (0.3)	4 (0.4)	10 (0.3)	12 (1.0)
Acute Myocardial Infarction	2 (0.2)	3 (0.2)	0	5 (0.1)	5 (0.4)
Atrioventricular Block Complete	0	1 (<0.1)	0	1 (<0.1)	0
Cardiogenic Shock	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Myocardial Infarction	0	1 (<0.1)	2 (0.2)	3 (<0.1)	5 (0.4)
Arteriosclerosis Coronary Artery	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Arrest	0	0	1 (0.1)	1 (<0.1)	0
Cardiac Failure	0	0	0	0	1 (<0.1)
Cardiac Failure Congestive	0	0	0	0	1 (<0.1)
General Disorders and Administration Site Conditions	0	1 (<0.1)	1 (0.1)	2 (<0.1)	2 (0.2)
Sudden Death	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Sudden Cardiac Death	0	0	0	0	1 (<0.1)
Investigations	19 (2.0)	29 (2.3)	18 (1.8)	71 (2.1)	19 (1.5)
Blood Creatine Phosphokinase Increased	19 (2.0)	28 (2.2)	17 (1.7)	69 (2.1)	19 (1.5)
Electrocardiogram ST Segment Abnormal	0	1 (<0.1)	0	1 (<0.1)	0
Blood Creatine Phosphokinase MB Increased	0	0	1 (0.1)	1 (<0.1)	0
Nervous System Disorders	5 (0.5)	6 (0.5)	6 (0.6)	17 (0.5)	10 (0.8)
Cerebrovascular Accident	3 (0.3)	2 (0.2)	3 (0.3)	8 (0.2)	2 (0.2)
Carotid Artery Stenosis	0	1 (<0.1)	1 (0.1)	2 (<0.1)	1 (<0.1)
Cerebellar Hemorrhage	0	1 (<0.1)	0	1 (<0.1)	0
Cerebral Hematoma	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Cerebral Infarction	1 (0.1)	1 (<0.1)	0	2 (<0.1)	0
Carotid Arteriosclerosis	0	0	0	0	1 (<0.1)
Carotid Artery Disease	1 (0.1)	0	0	1 (<0.1)	0
Cerebrovascular Disorder	0	0	0	0	1 (<0.1)
Hemorrhagic Stroke	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Ischemic Stroke	0	0	1(0.1)	1 (<0.1)	0
Transient Ischemic Attack	1 (0.1)	0	0	1 (<0.1)	5 (0.4)
Vascular Disorders	2 (0.2)	0	1 (0.1)	3 (<0.1)	0
Infarction	2 (0.2)	0	1 (0.1)	3 (<0.1)	0

Source: Applicant's "Response to Letter from the FDA, 11-Jan-2009", Table 2.4

As for the Custom MACE endpoint, no dose response is seen for the SMQ MACE endpoint (Table 15) where again a higher percentage of events is seen for comparators than for any dose of saxagliptin overall and for most of the studies individually.

Table 15 Incidence of SMQ MACE by Dose of Saxagliptin and by Study

ST Treatment Period					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	16/937 (1.7)	18/1269 (1.4)	19/1000 (1.9)	58/3356 (1.7)	25/1251 (2.0)
CV181008	1/55 (1.8)	3/47 (6.4)	0/63 (0)	9/315 (2.9)	1/108 (0.9)
CV181011	0/102 (0)	2/106 (1.9)	1/98 (1.0)	3/306 (1.0)	2/95 (2.1)
CV181013	5/195 (2.6)	5/186 (2.7)	NA	10/381 (2.6)	3/184 (1.6)
CV181014	5/192 (2.6)	1/191 (0.5)	5/181 (2.8)	11/564 (2.0)	3/179 (1.7)
CV181038	2/145 (1.4)	1/146 (0.7)	NA	3/291 (1.0)	1/74 (1.4)
CV181039	NA	0/320	13/658 (2.0)	13/978 (1.3)	6/328 (1.8)
CV181040	3/248 (1.2)	6/253 (2.4)	NA	9/501 (1.8)	8/267 (3.0)
CV181041	NA	0/20	NA	0	1/16 (6.3)
ST + LT Treatment Period (120 Day Safety Update Database)					
	Saxa 2.5 mg n/N (%)	Saxa 5 mg n/N (%)	Saxa 10 mg n/N (%)	All Saxa n/N (%)	Comparator n/N (%)
Pooled	28/397 (3.0)	37/1269 (2.9)	30/1000 (3.0)	100/3356 (3.0)	41/1251 (3.3)
CV181008	1/55 (1.8)	3/47 (6.4)	0/63 (0)	9/315 (2.9)	1/108 (0.9)
CV181011	0/102 (0)	4/106 (3.8)	2/98 (2.0)	6/306 (2.0)	4.95 (4.2)
CV181013	9/195 (4.6)	10/186 (5.4)	NA	19/381 (5.0)	4/184 (2.2)
CV181014	6/192 (3.1)	6/191 (3.1)	9/181 (5.0)	21/564 (3.7)	6/179 (3.4)
CV181038	3/145 (2.1)	1/146 (0.7)	NA	4/291 (1.4)	2/74 (2.7)
CV181039	NA	2/320 (0.6)	19/658 (2.9)	21/978 (2.1)	11/328 (3.4)
CV181040	9/248 (3.6)	11/253 (4.3)	NA	20/501 (4.0)	12/267 (4.5)
CV181041	NA	0/20 (0)	NA	0/20 (0)	1/16 (6.3)

The results for SMQ MACE, for both ST and ST+LT, show essentially no treatment difference with estimates of 0.85 to 0.96 (Table 16). The upper bounds for the 95% confidence intervals are less than or equal to 1.52 for all analyses so this data satisfies the 1.8 boundary but not the 1.3 boundary set by the guidance.

The interpretation of the SMQ MACE results compared to the Custom MACE results are complicated by the inclusion of the events defined by increased CPK in the SMQ endpoint. As noted earlier, the primary difference between the two endpoints is the inclusion of these events. Because more events of increased CPK occurred in the saxagliptin group than the comparator group (ST+LT: 2.1% versus 1.4%, respectively), the inclusion of these events shifts the estimate to the right (Custom MACE point estimate of 0.5→SMQ point estimate of 0.96). Excluding the PT for increased CPK, an analysis of first SMQ MACE events (ST+LT periods) yields an OR of 0.5 with 95% CI of 0.3 to 0.9, results comparable to the Custom MACE results.

Table 16 Overall Results for SMQ MACE

	Saxagliptin (N=3356)	Comparator (N=1251)
Patient-years		
ST	1295	458
ST+LT	3753	1289
Events (%)		
ST	58 (1.8%)	25 (2.0%)
ST+LT	100 (3.1%)	41 (3.2%)
Events/1000 pt-years		
ST	46	54
ST+LT	28	32
Study-stratified Estimate of Treatment Difference¹ (95% CI)		
Odds Ratio – Exact method		
ST	0.90 (0.55, 1.52)	
ST+LT	0.96 (0.65, 1.42)	
Incidence Rate Ratio		
ST	0.85 (0.52, 1.42)	
ST+LT	0.89 (0.61, 1.31)	
Risk Difference		
ST	-0.2% (-1.1%, +0.7%)	
ST+LT	-0.1% (-1.3%, +1.0%)	

1- Odds ratios under 1 and risk differences less than 0 favor saxagliptin.

The forest plot for SMQ MACE (Figure 6) shows the contribution of each study to the overall estimate of risk and that no single study shows significant increased or decreased risk of MACE events due to saxagliptin. The Kaplan-Meier curve (Figure 7) also provides further support for no treatment difference.

Figure 6 Forest Plot of SMQ MACE Odds Ratio Results – ST+LT

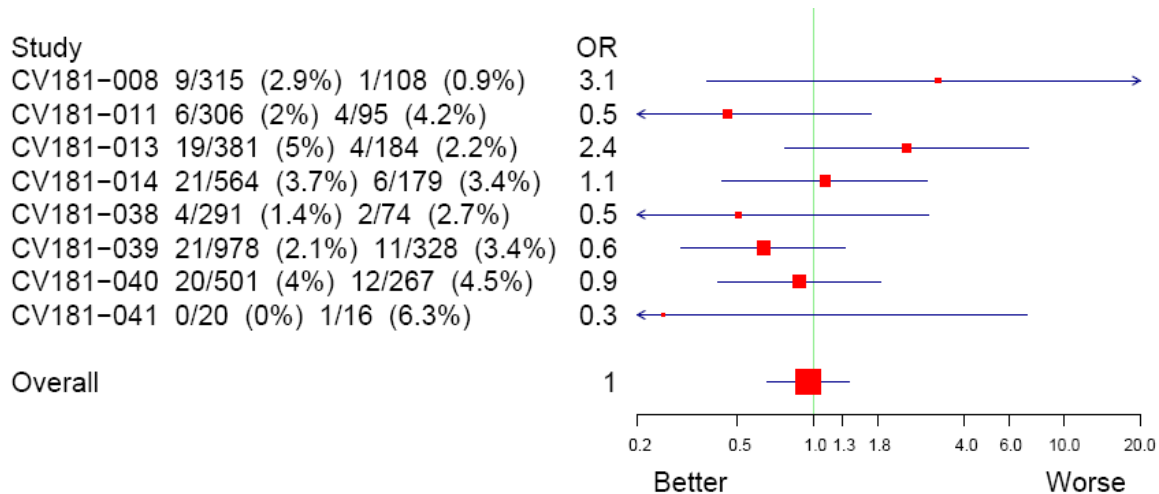
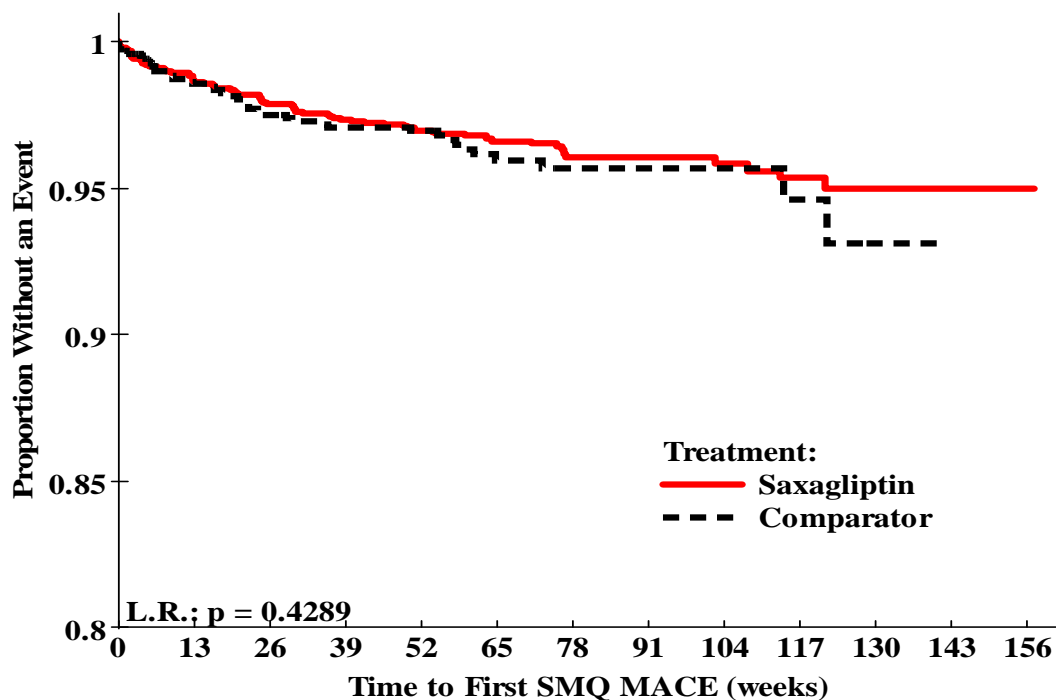


Figure 7 Kaplan-Meier Plot of SMQ MACE Results – ST+LT



Subgroup Analyses of Custom MACE

Exploratory analyses of subgroups defined by gender, age and type of trial were performed by FDA to assess the effect of saxagliptin in populations of differing CV risk. The Custom MACE endpoint was analyzed because this endpoint captures more relevant CV events. To obtain sufficient events in all subgroups, only the short-term plus long-term data were analyzed.

Two types of trials were examined; monotherapy and add-on trials. The monotherapy trials were Studies CV181008, CV181011, CV181038 and CV181041. The add-on trials were Studies CV181013, CV181014 and CV181040. All of these trials were placebo-controlled. The patient populations for these two types of trials differed with respect to duration of diabetes (~2 years for the monotherapy trials versus ~6 years for the add-on trials), randomized treatment exposure (~3 months longer for the add-on trials; see Figure 3 for details) and percentage of patients previously treated with anti-diabetic medications (0-15% for the monotherapy trials versus 100% for the add-on trials) [see Table 5 for additional demographic data on these trials]. These differences all suggest that a higher rate of CV events would be observed in the add-on trials than the monotherapy trials which is the case (Table 17).

Overall the Custom MACE results are consistent across these subgroups with no statistically significant evidence of interaction ($p > 0.10$); although the gender results are borderline significant. A test of interaction for treatment and gender for Broad SMQ MACE was statistically significant with $p = 0.03$.

The highest risk groups amongst these subgroups were males (control rate of 2.3%) and patients in the add-on trials (control rate of 1.8%). For both of these subgroups, the odds ratios were 0.5 or less and comparable to the overall estimate.

Table 17 Custom MACE results by subgroups for short-term plus long-term data

	Saxagliptin	Control	Stratified OR ¹ (95% CI)	Interaction p-value
Overall results	23/3356 (0.7%)	17/1289 (1.3%)	0.52 (0.3, 1.0)	
Gender				
Male	14/1659 (0.8%)	14/620 (2.3%)	0.4 (0.2, 0.9)	0.11
Female	9/1697 (0.5%)	3/631 (0.5%)	1.19 (0.3, 7)	
Age				
<65 years	17/2850 (0.6%)	15/1058 (1.4%)	0.43 (0.2, 0.9)	0.17
≥65 years	6/506 (1.2%)	2/193 (1.0%)	1.17 (0.2, 12)	
Type of trial				
Monotherapy ²	2/932 (0.2%)	1/293 (0.3%)	0.6 (0.1, 7.0)	>0.4
Add-on	13/1446 (0.9%)	11/630 (1.8%)	0.5 (0.2, 1.2)	

1- Odds ratios within subgroups are results of exact test stratified on study.

2- Of the 4 monotherapy studies, only one study had events (Study CV181011). To obtain an estimate for this exploratory analysis, the 4 studies were pooled.

Applicant's MACE analyses

MACE analysis using original NDA database

Upon receipt of the saxagliptin NDA, the FDA requested that the applicant (BMS) perform an analysis of MACE events (cardiovascular death, non-fatal MI, and non-fatal stroke) using the controlled Phase 2/3 database. The 10 mg open-label experience from Study CV181011 was not included in the analysis below; neither MACE events nor deaths were identified in the 10 mg open-label cohort. The total subject-years of exposure in the comparator group was 1015 compared with 2941 in the “all saxa” group. Therefore the overall pool had a ratio of approximately 3 subjects on saxagliptin to 1 on the comparator (see Table 7 for more details regarding patient exposure).

In order to perform this analysis, BMS used a list of selected PTs to search all adverse events (AEs) in the Phase 2b/3 clinical database (as of cutoff of NDA filing). This list was extracted from a pre-specified list of PTs developed for analyses of CV events for the NDA submission and was formulated as a subset of select MedDRA SMQs. The original pre-specified list was intended to identify CV AEs which were acute, ischemic, and clinically relevant. A subset of PTs from this list was then used to identify MACE events, which include stroke, myocardial infarction, and CV death. In general, in order to be chosen for the MACE list, PTs were required to represent events that were acute, symptomatic, and thromboembolic in nature. In addition, a clinical review of all deaths was performed to identify additional MACE events. Additional terms were identified by the Applicant that required clinical review prior to classification as a MACE event. These terms included: “infarction” unqualified, “silent MI”, and cerebral or coronary events which included the term “occlusion”, and serious cardiac rhythm disturbances.

Finally, in order to include any subject who died from a CV-related condition coded with a PT absent from the MACE PT list, a review of all deaths in Phase 2b/3 studies was performed by BMS. Every reported death in the Phase 2b/3 program was assessed to ascertain whether the underlying cause was CV-related based on the descriptive PT and a review of the case details. Deaths were classified as CV-related if the associated PTs either: 1) fell under the System-Organ-Class Cardiac Disorders; 2) were stroke-related; 3) were suggestive of sudden death; or 4) were related to other vascular events. The output used to summarize MACE events was then compared against this assessment to determine if any CV deaths were not included in the initial output. In the Phase 2b/3 program, there were 16 deaths reported as of the cutoff dates for the NDA submission. Of these 16, 11 were considered CV-related. Of these 11, 7 were already accounted for the programmed output. There were 4 remaining deaths (2 in the saxagliptin 10 mg group and 2 in the comparator group) that were not categorized as MACE events. Nevertheless, they are included in the table below.

The total numbers of randomized subjects with at least 1 MACE event, as defined by BMS, in the Phase 2b/3 program are shown in the table below. Please see Table 9 for a listing of preferred terms queried for the BMS MACE analysis and how these preferred terms compare to the FDA-requested preferred terms. Among the saxagliptin groups,

subjects treated with 10 mg had the highest percentage of MACE events (1%) which was equivalent to the comparator rate of 1%. The percentage of saxagliptin-treated patients who experienced a MACE event was lower than that of comparator-treated patients for all studies that reported MACE events, except for Study CV181011. An FDA analysis of the BMS-defined MACE events for all saxagliptin groups combined versus comparator yielded an OR of 0.5 with a 95% confidence interval of 0.2 to 1.2 (exact method stratifying on study). These results are consistent with the results seen for Custom MACE.

Table 18 Summary of MACE Events, as Defined by the Applicant, for Controlled Phase 2b/3 Pooled Population and by Phase 2b and 3 Studies

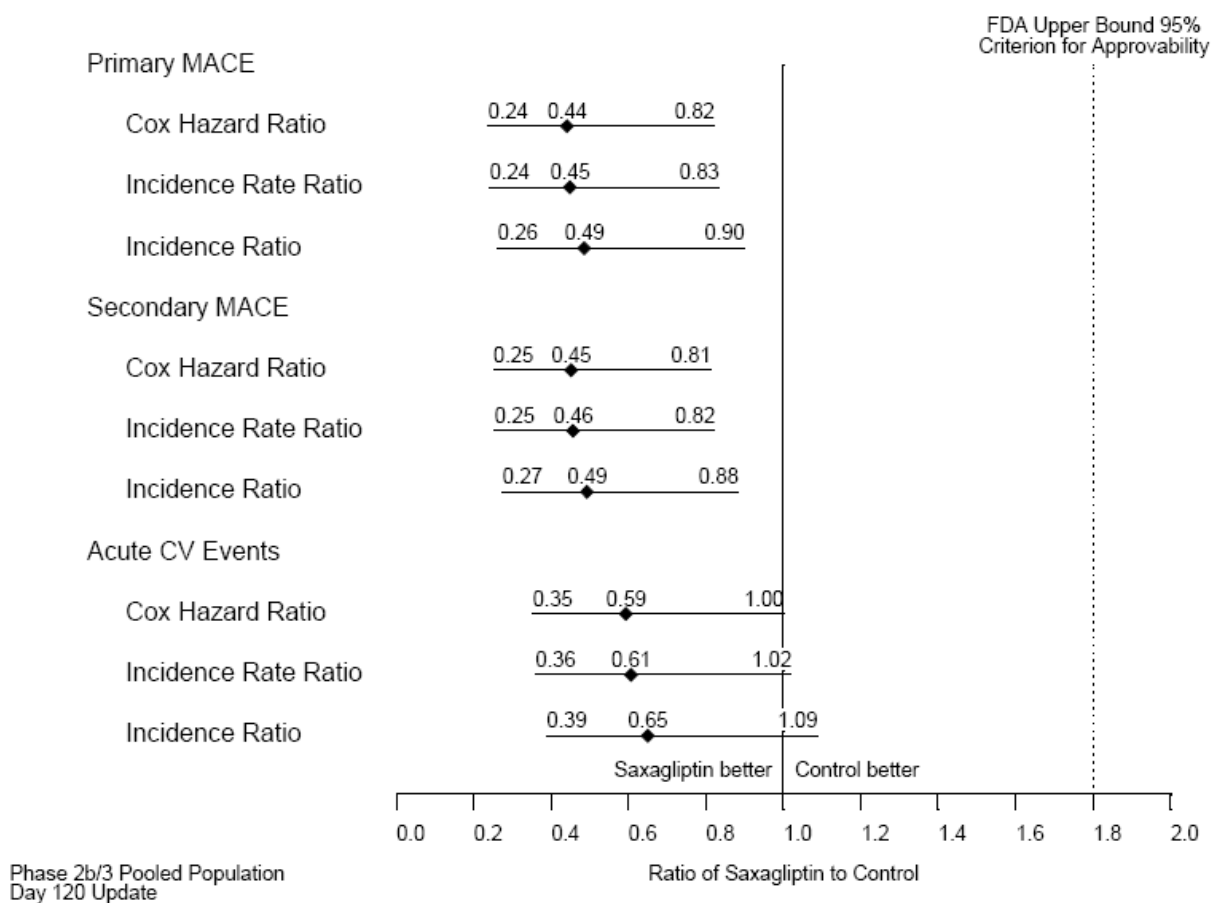
Population	Number (%)				
	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa*	Comparator**
	N=937	N=1269	N=1000	N=3356	N=1251
Pooled 2b/3	2 (0.2)	5 (0.4)	10 (1.0)	17 (0.5)	12 (1.0)
CV181008			None		
CV181011	0	2 (1.9)	0	2 (0.7)	0
CV181013	1 (0.5)	0	N/A	1 (0.3)	1 (0.5)
CV181014	0	1 (0.5)	4 (2.2)	5 (0.9)	3 (1.7)
CV181038			None		
CV181039	N/A	1 (0.3)	6 (0.9)	7 (0.7)	3 (0.9)
CV181040	1 (0.4)	1 (0.4)	N/A	2 (0.4)	5 (1.9)
CV181041			None		
*Includes 20-40 mg and 100 mg experience from CV181008					
**Includes metformin monotherapy from CV181039					
Source: Applicant's "Response to FDA day 74 Letter dated 12-Sep-2008", Ques. 7, Table 1					

Additional MACE analyses presented in Applicant's AC Briefing Document

The applicant performed additional analyses of MACE using the 120-day safety update database. In addition to a primary MACE analysis, the applicant defined several additional CV endpoints. These endpoints are described in the applicant's briefing document and are not repeated here. These results have not been thoroughly reviewed by FDA and, therefore, are only summarized here in a plot provided by the applicant, shown below. It is clear that these endpoints yield results consistent with the results seen for the original MACE endpoint and the FDA defined endpoint of Custom MACE.

Figure 8. Applicant's Figure from Briefing Document

Figure 6.5.4.4 Stratified Analyses of Sponsor-defined Cardiovascular Endpoints (120 Day Database) Phase 2b/3 Pooled Population



Total Mortality

In the phase 2/3 studies, a total of 16 deaths were reported during the ST and LT periods as of the data cutoff for LT interim clinical study reports. These include 2 subjects (0.2%) in the 2.5 mg saxagliptin group, 2 subjects (0.2%) in the 5 mg group, 3 subjects (0.3%) in the 10 mg group, 5 subjects (0.5%) in the placebo group, and 4 subjects (1.2%) in the metformin monotherapy group (Table 19). Of the 7 deaths in saxagliptin-treated subjects, 2 occurred during ST and 5 during LT. There were no deaths among subjects who received the 20 mg or 40 mg doses of saxagliptin, although exposure to these doses was of short duration. Seven additional deaths were reported in the Core Phase 3 studies during the reporting period of the 120-day Safety Update. These included 3 subjects in the saxagliptin groups, 3 subjects in the placebo group, and 1 in the metformin group. Short narratives for all deaths are included in Appendix 3.

Table 19 Deaths—Summary by Preferred Term for Saxagliptin Phase 2 and 3 Studies

(ST and LT as of data cutoff for LT interim clinical study reports)

Preferred Term	Saxa 2.5mg N=937	Saxa 5mg N=1269	Saxa 10mg N=1066	Saxa 20mg N=54	Saxa 40mg N=52	Saxa 100mg N=44	Placebo N=923	Placebo + Metformin N=328
Total Subjects with AE (%)	2 (0.2)	2 (0.2)	3 (0.3)	0	0	0	5 (0.5)	4 (1.2)
Acute MI	0	1 (<0.1)	0	0	0	0	0	1 (0.3)
Atrioventricular (AV) Block Complete	0	1 (<0.1)	0	0	0	0	0	0
Cardiogenic Shock	0	1 (<0.1)	0	0	0	0	1 (0.1)	0
Tetanus	0	1 (<0.1)	0	0	0	0	0	0
Arteriosclerosis Coronary Artery	0	0	1 (<0.1)		0	0	0	0
Cardiac Failure	0	0	0	0	0	0	0	1 (0.3)
Cardiac Failure Congestive	0	0	0	0	0	0	1 (0.1)	0
CVA	0	0	0	0	0	0	0	1 (0.3)
Hemorrhagic Stroke	0	0	0		0	0	1 (0.1)	0
Lung Neoplasm	0	0	1 (<0.1)	0	0	0	0	0
Myocardial Infarction (MI)	0	0	0	0	0	0	1 (0.1)	0
Pancreatic Neoplasm	0	0	0	0	0	0	0	1 (0.3)
Pneumococcal Sepsis	1 (0.1)	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	1 (0.1)	0
Pulmonary Embolism	0	0	1 (<0.1)	0	0	0	0	0
Road Traffic Accident	1 (0.1)	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	1 (0.3)
Sudden Cardiac Death	0	0	0	0	0	0	1 (0.1)	0
Sudden Death	0	0	1 (<0.1)	0	0	0	0	0

Summary and Discussion

The applicant, Bristol-Myers-Squibb Company, has submitted the results of eight Phase2/Phase 3 studies for the assessment of cardiovascular risk associated with saxagliptin. One of the goals of this assessment is to interpret the results in the context of the guidance entitled “Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” issued by FDA after submission of the saxagliptin NDA. These eight randomized, controlled, double-blind studies (Table 20) are comprised of two studies with 12-week ST treatment periods and six studies, considered the Core Phase 2b/3 studies, with 24-week ST treatment periods. The Core studies included four studies where saxagliptin was administered as monotherapy to patients largely naïve to previous anti-diabetic treatment, three studies where saxagliptin was added to anti-diabetic treatment in patients inadequately treated and one study where naïve patients were initiated on fixed-dose combination therapy of saxagliptin plus metformin.

**Table 20 Studies included in safety database to assess CV risk
(Core studies are shaded)**

Study	Design	Treatment Groups # randomized	
CV181008	Monotherapy Dose Response 12-week ST	Saxa 2.5mg	55
		Saxa 5mg	47
		Saxa 10mg	63
		Placebo	67
CV181041	Monotherapy Mechanism of action 12-week ST	Saxa 5mg	20
		Placebo	16
CV181011	Monotherapy Dose Response 24-week ST	Saxa 2.5mg	102
		Saxa 5mg	106
		Saxa 10mg	98
		Placebo	95
CV181038	Monotherapy QPM and QAM Dosing 24-week ST	Saxa 2.5mg	74
		Saxa 5mg	74
		Saxa 2.5/5mg	71
		Saxa 5mg qpm	72
		Placebo	74
CV181013	Add-on Saxa OL TZD 24-week ST	Saxa 2.5mg +TZD	195
		Saxa 5mg + TZD	186
		Placebo + TZD	184
CV181014	Add-on Saxa OL MET 24-week ST	Saxa 2.5mg + Met	192
		Saxa 5mg + Met	191
		Saxa 10mg + Met	181
		Placebo + Met	179
CV181040	Add-on Saxa OL Glyburide 24-week ST	Saxa 2.5mg + Gly	248
		Saxa 5mg + Gly	253
		Placebo + Gly	267
CV181039	Fixed Dose Combination with Metformin 24-week ST	Saxa 5mg + Met	320
		Saxa 10mg + Met	323
		Saxa 10mg	335
		Metformin	328

All studies included a 5 mg arm of saxagliptin, the proposed marketed dose. For the safety analyses performed by the applicant and FDA, the dose groups in each trial were combined so the exposure on saxagliptin is about 2-3 times greater than exposure to the comparator.

In seven of the eight trials, the comparator is placebo; the exception is the combination study (CV181039) where saxagliptin can be directly compared to metformin.

The patient populations did not vary greatly across these eight studies (see Table 5 for details); although patients entered in the add-on trials, on average, had been diagnosed with diabetes twice as long as the patients in the other trials and had a slightly higher baseline use of CV medication and thereby would be expected to comprise a higher risk CV population.

With the exception of Phase 2 Study CV181008, all studies entered patients who were rescued during short-term therapy or who completed short-term therapy into a long-term period where double-blind treatment was continued. Both the short-term data and the short-term plus long-term data were assessed for CV risk.

To assess CV risk, several major cardiovascular adverse event (MACE) endpoints were defined by FDA and by the applicant. All the definitions are compliant with the proposed CV endpoints described in the guidance. This document focused primarily on the endpoints defined by FDA: Custom MACE and SMQ MACE. These endpoints are described in detail on pages 14-18 of this document. The primary difference between these two endpoints is that SMQ MACE is a broader endpoint that includes Custom MACE events and additional events defined by the Standardized MedDRA Queries (SMQ) for “Myocardial Infarction” and “Central Nervous System Haemorrhages and Cerebrovascular Accidents”. A total of 101 additional events were observed for SMQ MACE during the ST+LT period with the majority of those events (in both treatment groups) being “CPK increased” (see Tables 10 and 14 for details on the preferred terms observed for both endpoints). The other additional SMQ events were Nervous System Disorders and Vascular Disorders. Note that all Cardiac Disorders identified for SMQ MACE were also identified for Custom MACE.

An additional MACE endpoint reviewed by FDA was a MACE endpoint defined by BMS following a request from FDA at the time of the filing of the NDA. For comparison of the preferred terms queried for this endpoint compared to Custom MACE and SMQ MACE, see Table 9. This endpoint was analyzed using the originally submitted database.

Analyses of the FDA endpoints of Custom MACE and SMQ MACE and the MACE endpoint initially defined by BMS all yielded estimates of the common odds ratio (computed using exact methods) less than 1 suggesting reduced risk of MACE due to saxagliptin compared to comparator; only the results for Custom MACE ST are statistically significant (Table 21).

The inclusion of a PT for “increased CPK” in the SMQ endpoint dilutes the effect of saxagliptin seen for Custom MACE and results in an estimate close to 1 and upper bounds for the confidence interval greater than 1.3 (a boundary suggested by the guidance to be adequate for demonstrating a lack of increased CV risk).

Table 21 Summary of MACE Results*

	Saxagliptin (n=3356)	Comparator (n=1251)	Common Odds Ratio Stratified on Study (95% CI)
Initial BMS MACE ST+LT	17 (0.5%)	12 (1.0%)	0.5 (0.2, 1.2)
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; for the initial BMS analysis, the originally submitted database was used.

The low event rates seen for the comparator group suggest that the population studied was a low CV risk Type 2 diabetic population. Generally MACE annual rates of about 3% or higher would be expected in a broader population that included high-risk patients (e.g. the Type 2 diabetics in the PROactive Study and the Heart Protection Study). For this meta-analysis, the Custom MACE rate for the ST+LT period (Median duration of about 60 weeks) of the comparator is only 1.3%. To address any concerns about applicability of the results in a higher risk population, subgroup analyses were performed (see Table 17) and the Custom MACE results were found to be consistent with the overall results for groups with comparator rates of about 2%.

In summary, all the MACE results produced by FDA and the applicant meet the guidance criterion of an upper bound on the 95% confidence interval of the odds ratio of less than 1.8. Furthermore, the Custom MACE results showed upper bounds for the CI less than 1.3, regardless of analytical approach. The implication of these results to further assessment of CV risk for saxagliptin as proposed by the FDA guidance will be an important point of discussion at the advisory committee meeting.

Appendix 1. Listing of Completed Phase 1 & 2 Clinical Studies & 3 Ongoing Studies
These studies were not included in the database for the analysis of cardiovascular events.

Study Number	Type of Study	Study Design and Type of Control	Target Population /Number of Subjects	Objective(s) of the Study	Dosage Regimen	Treatment Duration
181001	Single ascending dose	Single ascending dose, placebo-controlled	Healthy N=70	Safety, PK, PD, food effect	Saxa 1, 2.5, 5, 10, 20, 30, 50, 75, or 100mg PO	<i>Single dose</i>
181002	Multiple ascending dose	Multiple Ascending dose, randomized, placebo-controlled	Type 2 DM N=40	Safety, PK, and PD	Saxa 2.5, 5, 15, 30, or 50mg PO	<i>14 days</i>
181003	Relative Bio-availability	Open-label, randomized, 2-period, 2-treatment cross-over	Healthy N=16	Relative bioavailability, PK, safety	Saxa 1 x 40mg tablet versus 2 x 20mg tablets; placebo	<i>Single dose</i>
181004	¹⁴ C ADME	Open-label single dose	Healthy N=6	PK, mass balance, metabolism, safety	Saxa 50mg, ¹⁴ C metabolism	<i>Single dose</i>
181005	Drug interaction	Open-label single sequence	Healthy N=15	Drug-drug interaction with ketoconazole	Saxa 100mg qd with 200mg q12h ketoconazole	<i>12 days</i>
181010	Multiple ascending dose	Multiple ascending dose, randomized, double-blind, placebo-controlled	Healthy N=50	Safety, PK, and PD	Saxa 40, 100, 150, 200, 300, or 400 mg	<i>14 days</i>
181017	Drug interaction	Open-label, randomized, 3-period, 3-treatment, cross-over study balanced for residual effects	Healthy N=18	Drug-drug interaction with met, safety	Saxa 100mg and Met 1000mg	<i>Single dose</i>
181018	Age/gender	Open-label, single dose, 2 x 2 factorial design	Healthy N=56	Effect of age and gender on PK, safety	Saxa 10mg	<i>Single dose</i>

Study Number	Type of Study	Study Design and Type of Control	Target Population /Number of Subjects	Objective(s) of the Study	Dosage Regimen	Treatment Duration
181019	Renal Impairment	Open-label, parallel-group single dose	Renally impaired and healthy subjects	PK of saxa in subjects with renal impairment, safety	Saxa 10mg	<i>Single dose</i>
181020	Hepatic Impairment	Open-label, parallel-group single dose	Hepatically impaired and healthy subjects N=36	PK of saxa in subjects with hepatic impairment, safety	Saxa 10mg	<i>Single dose</i>
181021	Relative Bioavailability	Open-label, randomized, 2-period, 2-treatment cross-over	Healthy N=16	Relative bioavailability and safety	1 x 5mg saxa tablet versus 1 x 5mg saxa capsule	<i>Single dose</i>
181022	Safety	Open-label, randomized, 3-sequence	Healthy N=36	Effects of ketoconazole and saxa on lymphocyte count; safety	Ketoconazole 200mg q12h plus Saxa 5 or 20mg	<i>12 days</i>
181026	Drug interaction	Open-label, randomized, 3-period, 3-treatment, cross-over study balanced for residual effects	Healthy N=30	Drug-drug interaction with glyburide; safety	Saxa 10mg plus 5mg glyburide	<i>5 days</i>
181027	Drug interaction	Open-label, randomized, 3-period, 3-treatment, cross-over	Healthy N=14 (0 completed, terminated early)	Drug-drug interaction with digoxin, safety	Multiple regimens using saxa 5mg and digoxin	<i>30 days, terminated early due to dosing error</i>
181028	Drug interaction	Open-label, non-randomized, sequential	Healthy N=30	Drug-drug interaction with pioglitazone	Saxa 10mg and pioglitazone 45mg	<i>13 days</i>
181031	Safety, PK	Double-blind, multiple-dose, randomized, parallel-group, placebo-controlled	Healthy N=48	Effect of saxa on lymphocyte count and cyanide formation; safety	Saxa 10 or 40mg qd	<i>23 days</i>

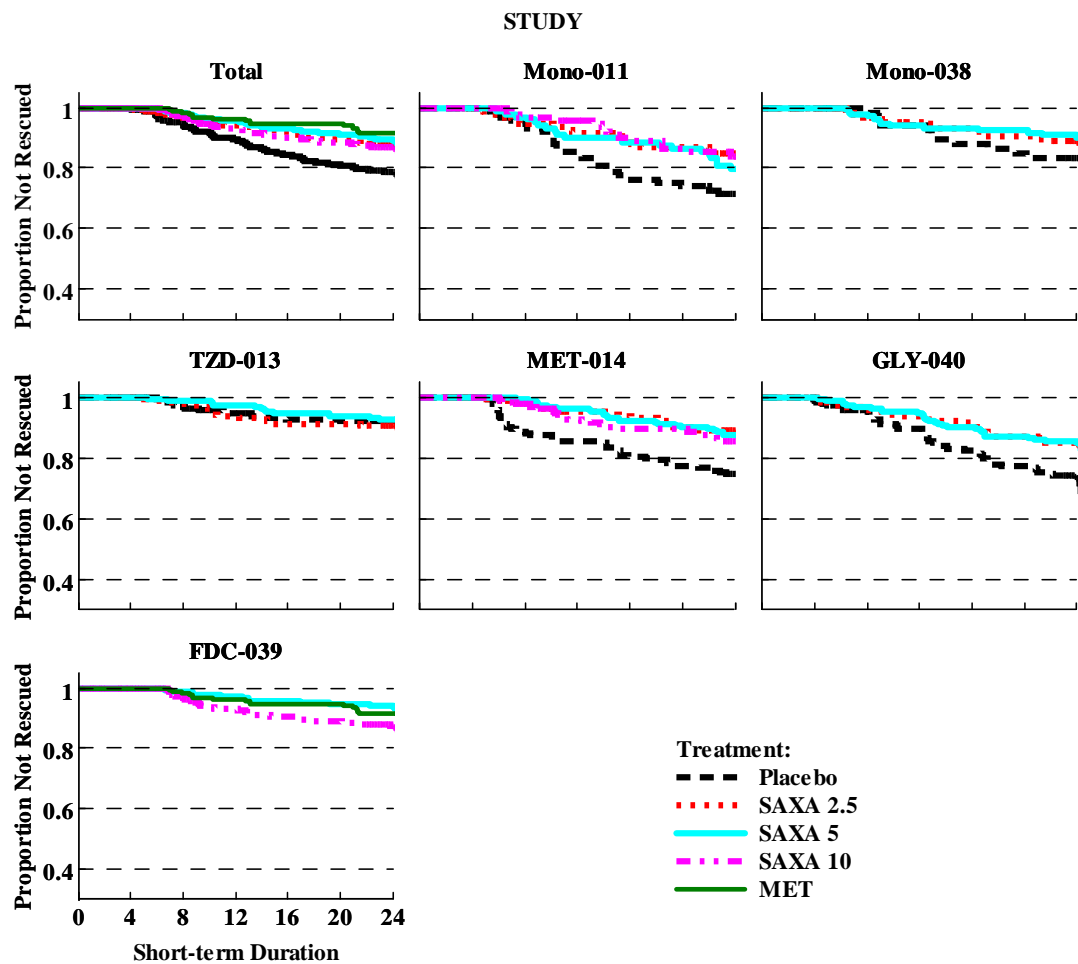
Study Number	Type of Study	Study Design and Type of Control	Target Population /Number of Subjects	Objective(s) of the Study	Dosage Regimen	Treatment Duration
181032	Thorough QTc study	Randomized, double-blind, placebo-controlled, 4-period, 4-treatment, cross-over	Healthy N=40	ECG effects of saxa; PK	Saxa 10 or 40mg qd, Moxifloxacin 400mg qd	16 days
181033	Drug interaction	Open-label, non-randomized, sequential	Healthy N=24	Drug-drug interaction with simvastatin	Saxa 10mg qd, Simvastatin 40mg qd	12 days
181034	Definitive Food Effect	Open-label, randomized, 2-period, 2-treatment, crossover	Healthy N=14	Effect of food on the PK of saxa; safety	Saxa 10mg, fasting vs non-fasting	Single dose
181035	Gastric Acid Controller Interaction	Open-label, randomized, 5-treatment, 5-period, unbalanced 3-way crossover	Healthy N=15	Effect of Maalox Max®, famotidine and omeprazole on the PK of saxa	Saxa 10mg, Maalox Max® 30 ml, famotidine 40mg, omeprazole 40mg	11 days
181036	Relative Bioavailability	Open-label, randomized, 2-period, 2-treatment, crossover	Healthy N=12	Relative bioavailability and safety	Saxa 2 x 5mg tablet versus 1 x 10mg tablet	Single dose
181037	Relative Bioavailability	Open-label, randomized, 2-period, 2-treatment, crossover	Healthy N=16	Relative bioavailability, PD; safety	Saxa 5mg tablet versus Saxa 5mg capsule	Single dose
181052	Drug interaction	Open-label, randomized, 3-period, 3-treatment, crossover	Healthy N=14	Drug-drug interaction with digoxin; safety	Saxa 2 x 5mg, digoxin on Days 1-7	19 days
181053	Drug interaction	Open-label, non-randomized, single-sequence	Healthy	Drug-drug interaction with diltiazem; safety	Saxa 10mg qd, diltiazem, 360mg qd	10 days
181059	Drug interaction	Open-label, non-randomized, single-sequence	Healthy	Effect of rifampin on PK of saxagliptin	Saxa 5mg on Day 1, rifampin Days 2-6, Saxa 5mg + rifampin on Day 7	7 days, ongoing

Study Number	Type of Study	Study Design and Type of Control	Target Population /Number of Subjects	Objective(s) of the Study	Dosage Regimen	Treatment Duration
262-07-001	Safety, tolerability, PK and PD	PBO-controlled, single (ascending, 2-periods) and multiple dose study	Healthy	Safety, tolerability, PK, and PD	Single dose: Saxa 1, 2.5, 5, 10 or PBO, fasting or 30 min before meal Multiple dose: Saxa 10mg 30 min before meal	<i>Single dose and multiple dose</i>
181054*	Safety and efficacy	Randomized, double-blind, parallel,-group, active-controlled	Type 2 DM	Safety and efficacy	Saxa 5mg + OL Met 1500-3000mg; or glipizide 5-20mg + OL Met	<i>52 weeks with 52-week extension, ongoing</i>
181056*	Safety and efficacy	Randomized, double-blind, parallel,-group, active-controlled	Type 2 DM	Safety and efficacy	Saxa 5mg + OL Met 1500-3000mg; or sitagliptin 100mg + OL Met 1500-3000mg	<i>18 weeks, ongoing</i>
181062*	Safety and efficacy	ST: Randomized, parallel-group, double-blind, placebo-controlled LT: observational	Type 2 DM with moderate, severe, and end-stage renal impairment	Safety and LT efficacy	ST: Saxa 2.5mg or PBO LT: Saxa 2.5mg or PBO	ST: 12 weeks, ongoing LT: 40 weeks, ongoing

Abbreviations: ADME=Absorption, Distribution, Metabolism, and Elimination; Gly=Glyburide; LT=long-term; Met=metformin; min=minutes; PBO=placebo; PD=Pharmacodynamics; PK=Pharmacokinetics; qd=once daily; qam=once in the morning; qpm=once in the evening; Saxa=saxaglipitin; ST=short-term; SU=sulfonylurea; T2DM=type 2 diabetes mellitus; wks=weeks

*No data included in NDA submission

Appendix 2 Proportion of patients not rescued for all studies combined and by study



Appendix 3 Brief Narratives of Deaths

Saxagliptin-treated subjects - ST

Subject CV181038-85-572, a 47 year old white male with a history of splenectomy secondary to trauma was in the saxagliptin 2.5mg group, died on Day 54 with a recent history of upper respiratory symptoms 5 days prior. He had not received Pneumovax. On Day 54, the subject awoke with fever and chills and presented to the emergency room (ER) with abdominal pain, hypotension, and bradycardia. He was treated for **sepsis**, but his clinical condition deteriorated and he died despite cardiopulmonary resuscitation. Post-mortem results from blood cultures obtained in the ER demonstrated *Streptococcus pneumoniae*. The investigator characterized the death as unrelated to study medication.

Subject CV181013-74-386, a 66 year old white female in the saxagliptin 2.5mg group, died in an **automobile accident** on Day 102. She encountered slippery road conditions, and the car lost control and spun into oncoming traffic. She died from trauma. The investigator characterized the event leading to death as not likely related to study medication.

Saxagliptin-treated subjects - LT

Subject CV181014-171-778, a 48 year old white male in the saxagliptin 10mg group, had a history of smoking, was diagnosed with a Grade 3 **pulmonary neoplasm** on Day 431. He had presented with weight loss, dysphagia, right eyelid ptosis, and leukocytosis. He was hospitalized on Day 449 for a bronchoscopy. However, on the same day, he experienced a **pulmonary embolism** and died. This occurred prior to rescue and 14 days after study medication was discontinued. The investigator characterized the event leading to death as unrelated to study medication.

Subject CV181039-148-943, a 57 year old white male in the saxagliptin 10mg group, had a medical history of hypertension, **coronary artery disease**, previous myocardial infarction, stable angina, obesity, hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia. According to the subject's relative, on Day 294, the subject died suddenly. The investigator characterized the event leading to death as unrelated to study medication.

Subject CV181039-232-2798, a 55 year old Asian male in the saxagliptin 10mg+metformin group, died of "**sudden death**" on Day 254. He had a medical history of poorly controlled hypertension and overweight. He was noted to have a right bundle branch block on Days 101 and 180. On the day of his death, the subject reported feeling unwell and fell to the ground. There was no medical observation of the death or medical intervention performed. The investigator characterized the event leading to death as possibly related to study medication.

Subject CV181040-100-1810, a 68 year old male in the saxagliptin 5mg group, died on Day 214 of **cardiogenic shock**. He had a medical history of diabetic neuropathy, hypertriglyceridemia, and hypertension. On Day 213, he experienced an **acute myocardial infarction, third-degree atrioventricular block**, and cardiogenic shock. ECG showed ST elevation in lead II and III with third degree AV block. Cardiac catheterization showed complete obstruction of the right main coronary artery. The investigator characterized the events leading to death as unlikely related to study medication.

Subject CV181039-155-2139, a 49 year old Asian man in the saxagliptin 5mg + metformin group, died on Day 230 of acute respiratory failure secondary to **tetanus**. With a medical history of hypertension, he sustained a puncture wound and was treated with amoxicillin/clavulanate and

tetanus toxoid injection. According to the subject's wife, he was not compliant with the injectable medication. The subject was admitted to the hospital on Day 229 and died the following day. The investigator characterized the event leading to death as unrelated to study medication.

Saxagliptin-treated subjects – Safety Update

Subject CV181014-175-1104, a 63 year old male in the saxagliptin 2.5mg group, died on Day 777 after being hospitalized with a **hemorrhagic stroke** on Day 756. Additional information received after database lock indicated that he received study drug within 30 days prior to the event.

Subject CV181013-229-433, a 63 year old female in the saxagliptin 5mg group (also receiving pioglitazone 45mg daily) died on Day 509 of **sudden cardiac arrest**. She had a serious adverse event of atrial fibrillation with rapid ventricular response and was hospitalized on Day 494. On Day 497, she developed a cerebellar hemorrhage.

Subject CV181039-237-1549, a 71 year old male in the saxagliptin 10mg group, died of **cardiac arrest** in a taxi while on his way to the hospital for chest pain on Day 377.

Placebo-treated subjects - ST

Subject CV181014-171-1341, a 35 year old white male in the placebo group, died of **cardiogenic shock** on Day 157. He had a history of hypertension and hypertriglyceridemia. The investigator characterized the death as unrelated to study medication.

Subject CV1810040-68-1424, a 58 year old Asian male in the placebo group, died of **sudden cardiac death** on Day 112. He had a medical history of coronary artery disease and cerebrovascular disease. The investigator characterized the death as unlikely related to study medication.

Placebo-treated subjects - LT

Subject CV181014-13-254, a 48 year old white male in the placebo group, died of **congestive heart failure** on Day 405. He had a history of obesity, hyperlipidemia, and tobacco use. The investigator characterized the death as unrelated to study medication.

Subject CV181040-65-981, a 54 year old Asian male in the placebo group, died of severe **pneumonia** on Day 424. He had a history of tobacco use and pulmonary tuberculosis. The investigator characterized the death as unrelated to study medication.

Subject CV181040-127-89, a 62 year old female in the placebo group, died of an **acute hemorrhagic stroke** on Day 201. She had a medical history of hypertension and stroke. The investigator characterized the death as unrelated to study medication.

Placebo-treated subjects – Safety Update

Subject CV181011-125-649, a 74 year old female in the placebo group, died of **cerebral hemorrhage** on Day 861. This followed a serious adverse event of myocardial infarction on Day 852. A CT scan on Day 854 showed cerebral hemorrhage.

Subject CV181040-65-981, a 54 year old male in the placebo group, was reported to have died on Day 424 of **pneumonia**. He had an extensive smoking history and was diagnosed with pulmonary tuberculosis in 1996 with reactivation in 2004.

Subject 181040-127-1070, a 64 year old white male in the placebo group, died on Day 452 of an **acute myocardial infarction**. He had a history of ischemic cardiomyopathy, and he died at home during the night.

Metformin-treated subjects- ST

Subject CV181039-60-1617, a 65 year old white male in the metformin group, was found dead in his home on Day 144 (death due to **cardiac failure**). He had a medical history of hypertension and myocardial infarction. The investigator characterized the death as unrelated to study medication.

Subject CV181039-140-1597, a 60 year old white male in the metformin group, died of an **acute myocardial infarction** on Day 6. He had a history of hypertension and myocardial infarction. The investigator characterized the death as unrelated to study medication.

Subject CV181039-141-1059, a 62 year old white male in the metformin group, had a **cerebrovascular accident** on Day 130 and underwent drainage for an intracerebral hematoma. He died on Day 135. The investigator characterized the death as unrelated to study medication.

Metformin-treated subjects - LT

Subject CV181039-193-688, a 55 year old female in the metformin group, died due to **pancreatic neoplasm** and **sepsis** on unspecified day. She had a medical history of obesity and hypercholesterolemia. The investigator characterized the pancreatic neoplasm as possibly related and sepsis as unrelated to study medication.

Metformin-treated subjects – Safety Update

Subject CV181039-222-1033, a 58 year old male in the metformin monotherapy group, was reported to have **sudden death** on Day 383.

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Ilan Irony at 301-796-2290.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2008
Clinical/Medical**

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2008
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Guidance for Industry¹
Diabetes Mellitus: Developing Drugs and Therapeutic
Biologics for Treatment and Prevention

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment and prevention of diabetes mellitus. The intention of this guidance is to serve as a focus for continued discussions among the review divisions, pharmaceutical sponsors, academic community, and the public.² The organization of the guidance parallels the development plan for a particular drug or biologic. In the following discussion, we briefly describe type 1 and type 2 diabetes mellitus and treatment goals, discuss issues relevant to preclinical development, and then provide guidance on issues related to trial design, endpoints appropriate for different phases of development, and eligible populations. These issues are addressed for both type 1 and type 2 diabetes mellitus.

Although this guidance focuses more on the development of drug and therapeutic proteins to target the metabolic control of blood glucose in patients with diabetes, it also provides guidance on the development of products intended to prevent diabetes mellitus in high-risk individuals. Since the development of products for the prevention of diabetes is a relatively novel area, it is possible that specific guidances will be developed in the future for this topic as regulatory experience accrues. Therapeutic approaches to mitigate or reverse other clinical or pathophysiological hallmarks of what is often termed the metabolic syndrome are not addressed in this guidance.

¹ This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of diabetes drug or biological products. The FDA/NIH Joint Symposium on Diabetes, held on May 13 and 14, 2004, in Bethesda, Maryland, gathered relevant perspectives from academia and industry on issues covered in this guidance.

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In addition, we recognize other important topics surrounding the treatment and prevention of diabetes mellitus. However, the following discussions are beyond the scope of this guidance.

- A comprehensive treatment strategy involves dietary changes and interventions other than medications.
- Highly desirable treatments specifically targeted to have direct effects in preventing end organ damage and diabetes-associated acute and chronic complications.
- Significant advances in the development of treatments for diabetes have been made through experimental approaches other than drugs or therapeutic proteins, such as transplantation of pancreata, pancreatic islet cells, stem cells that may differentiate into insulin-producing cells, and closed-loop devices (or artificial pancreas) that constantly monitor blood or interstitial glucose and adjust automated insulin delivery via a pump accordingly.
- The expansion of available choices in diagnostic devices that allow accurate and instantaneous glucose measurements, continuous glucose monitoring, and the identification of parameters of glucose metabolism characterizing states of insulin resistance has been significant to patients and health care professionals.

Advice on the development of specific products for preventing or treating complications of diabetes (e.g., diabetic peripheral neuropathy) can be sought from the relevant review division and other existing guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.³ Instead, this guidance focuses on specific drug development and trial design issues that are unique to the study of diabetes mellitus, as measured by changes in hemoglobin A1c (HbA1c, glycosylated hemoglobin, or glycohemoglobin). Reductions in HbA1c directly reflect improvements in glycemic control. Therefore, HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus.

The FDA recognizes that diabetes mellitus is associated with an increased risk of macrovascular complications and that reducing long-term cardiovascular complications in patients with diabetes should be an important goal of disease management. However, a premarketing recommendation to demonstrate macrovascular risk reduction in the absence of a signal for an adverse cardiovascular effect may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy. A reasonable approach may be to conduct long-term cardiovascular studies post-approval in an established time frame. We recommend that the design of such trials be discussed with the FDA and perhaps with clinical

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

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trialists and experts in endocrinology and cardiology. This approach is beyond the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND TREATMENT GOALS

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although there are several drug treatments currently available (see Appendix C), the FDA recognizes the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs, therapeutic biologics, and devices).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure and has a heritable basis). Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial (DCCT)⁴ has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy. Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.⁵ There are also reasonably strong data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control, although macrovascular risk reduction in this patient population is less conclusive.⁶

⁴ N Engl J Med, 1993, 329:977-986

⁵ Diabetes, 2006, 55:3556-3565

⁶ Lancet, 1998, 352:837-853 and 854-865

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Glycemic control in these studies has been based on changes in HbA1c. This surrogate endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. In addition, there is a growing recognition that addressing cardiovascular disease risk factors, such as hypertension, smoking, and dyslipidemia, in patients with diabetes is particularly important, as diabetes is now considered an atherosclerotic heart disease equivalent.

III. DIAGNOSING DIABETES MELLITUS

Based on studies that have established a relationship between plasma glucose concentrations, measures of glycemic exposure, and risk of diabetic retinopathy, the following criteria have been adopted for the diagnosis of diabetes mellitus:

- Fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L)
- Plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) at 2 hours following ingestion of 75 g anhydrous glucose in an oral glucose tolerance test
- Random plasma glucose greater than 200 mg/dL (11.1 mmol/L) in a person with symptoms of diabetes

These criteria were recommended by the American Diabetes Association (ADA) and the World Health Organization (WHO) in 1997 and 1998, respectively.

Other important definitions include:

- Impaired glucose tolerance: a plasma glucose equal to or greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at 2 hours in the oral glucose tolerance test
- Impaired fasting glucose: fasting plasma glucose (FPG) equal to or greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL
- Gestational diabetes mellitus (GDM):
 - According to the ADA criteria, GDM is detected based on two or more values meeting or exceeding any of the following threshold values during a 75- or a 100-g oral glucose tolerance test:
 - FPG greater than or equal to 95 mg/dL (5.3 mmol/L)
 - Plasma glucose greater than or equal to 180 mg/dL (10 mmol/L) at 1 hour
 - Plasma glucose greater than or equal to 155 mg/dL (8.6 mmol/L) at 2 hours
 - Plasma glucose greater than or equal to 140 mg/dL (7.8 mmol/L) at 3 hours (the optional 3-hour time point only applies to the 100-g test)
 - GDM is diagnosed by the WHO criteria if FPG is greater than or equal to 126 mg/dL (7.0 mmol/L) or if the 2-hour glucose after a 75-mg oral glucose load is greater than or equal to 140 mg/dL (7.8 mmol/L)

Impaired fasting glucose and impaired glucose tolerance have recently gained importance because they identify groups of people at high risk for developing overt diabetes mellitus over

time, and because recent studies have demonstrated reductions in the progression to overt disease in these groups with specific therapeutic interventions. These individuals, along with women who have had a history of gestational diabetes, have been targeted for clinical evaluation of diabetes prevention.

IV. PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES⁷

Preclinical development often includes pharmacology studies in which efficacy is assessed in animal models appropriate to the diabetes type being targeted for therapy. Toxicology studies for antidiabetic therapies generally should be conducted in the standard nondiabetic animal models.

A. Type 1 Diabetes Mellitus

In preclinical models that most closely mimic type 1 diabetes in humans, animals manifest spontaneous insulinitis and progressive beta-cell destruction. Non-obese diabetic (NOD) mice and diabetes-prone BioBreeding (BB) rats are the most commonly used rodent models for type 1 diabetes, in which proof-of-concept studies of prospective therapeutic agents can be conducted. Such studies examine parameters relevant to the treatment of human disease, such as preservation of beta cells and insulin secretory function and fasting and postprandial levels of C-peptide and glucose. Streptozotocin-induced diabetes in rats is a predictable metabolic model of human type 1 diabetes, but does not involve an autoimmune mechanism, and, therefore, should not be used in preclinical studies of immune-directed diabetes prevention strategies.

NOD mice develop type 1 diabetes by an autoimmune disease similar to humans. In these mice, approximately 90 percent of females and 60 percent of males become hyperglycemic and develop diabetes by 12 months of age.

Approximately 90 percent of mature diabetes-prone BB rats develop diabetes. Diabetes-resistant BB rats constitute a variant that develop type 1 diabetes after some environmental insult (e.g., Kilham rat viral infection).

B. Type 2 Diabetes Mellitus

Animal models of type 2 diabetes are characterized by insulin resistance, hyperglycemia, and hyperinsulinemia. Some of the most frequently used models of type 2 diabetes are the leptin-deficient mouse (*ob/ob*), the leptin-receptor-deficient mouse (*db/db*), the obese Zucker rat (*fa/fa*), the Wistar Kyoto rat (*fa/fa*), and knockout mice lacking relevant targets, such as insulin receptors or glucose transporter 4 genes.

For all peroxisome proliferator-activated receptor (PPAR) agonists, 2-year carcinogenicity evaluations in rats and mice should be conducted before the initiation of clinical studies longer than 6 months in duration, based on their known carcinogenic potential as a class. Additionally, for PPAR drugs with gamma agonist activity, the maximum tolerated dose for carcinogenicity

⁷ See 21 CFR part 58 for the FDA's good laboratory practices for conducting nonclinical laboratory studies.

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assessment should be defined as the dose that results in a 20 to 25 percent increase in heart weight in rodents in the 13-week dose finding studies. This recommended dose limitation is designed to prevent excess cardiac mortality in the 2-year bioassay secondary to fluid accumulation and cardiomegaly. Refer to Appendix A for further details on this issue.

C. Insulins and Insulin Analogues

In vitro studies of insulins and insulin analogues can be useful for describing insulin receptor binding affinities and dissociation rates, receptor autophosphorylation, phosphorylation of signaling elements, and promotion of mitogenesis. In addition, for insulin analogues, affinity to the insulin receptor relative to other targets of insulin action, such as the insulin-like growth factor 1 receptor, should be characterized and compared to that found with native-sequence human insulin.

V. CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES⁸

A. Trial Design and Conduct

1. Optimization of Glucose Control and Diabetes-Associated Comorbid Conditions

Individualization of therapy is essential to optimum control of glycemia in patients with diabetes. Consequently, some studies permit use of other antidiabetic therapies before randomization to ensure enrollment of patients whose diabetes control will be acceptable for clinical investigational purposes. Such studies often allow entry of patients using a specific class of antidiabetic drugs (e.g., baseline metformin therapy in patients with type 2 diabetes), to which either the investigational drug (or biologic) or a placebo will be added during randomization. Addition of new noninvestigational drugs or substantial changes in the dose of permissible baseline drug therapy after randomization may confound the results and interpretability of both efficacy and safety. For the results to be interpretable, any changes to these other therapies should be carefully documented.

When planning exploratory phase 2 studies, we recommend that sponsors include a run-in period before randomization to allow for diabetes education and for optimization of compliance with diet and exercise. This 6- to 8-week run-in period also is intended to allow for stabilization of parameters of metabolic control (e.g., HbA1c, fructosamine), so that the magnitude of the effect of different doses of the product can be most accurately estimated. Absence of this run-in period can result in overestimation of the *real world* treatment effects, given the intensive reinforcement of hygienic measures and compliance during clinical trials that is not reflected in typical treatment settings. In addition, placebo run-in periods in phase 3 studies can help screen out noncompliant subjects. We recommend providing efficacy data with a new product that result from rigorously designed studies.

⁸ See 21 CFR parts 312, 50, and 56 for regulations regarding investigational new drug applications and human subject protection, including informed consent.

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Adequate control of diabetic comorbidities in accordance with current standards of care should be incorporated in the criteria for eligibility in the study protocol. The addition of therapies to control diabetic comorbidities after randomization should be carefully documented (as should be the use of these therapies at baseline), because these therapies may confound the interpretation of both safety and efficacy of the investigational drug or biologic.

Improvement in HbA1c has become the standard surrogate outcome measure in many trial designs for a variety of therapies. In patients with diabetes, the following situations also can be considered a benefit of therapy: 1) a meaningful reduction of insulin requirements (in either type 1 or type 2 diabetes), or 2) a reduction in the number or doses of oral antidiabetic agents (in type 2 diabetes mellitus), both in the context of stable or improved HbA1c. Even though HbA1c is appropriate as a surrogate endpoint in many study designs, documented improvement in a serious morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive evidence of benefit for drugs in which substantial safety issues or questions arise (see sections V.B., Study Assessments and Endpoints, and V.E., Sample Size and Study Duration, for additional considerations).

2. Type 1 Diabetes Mellitus

As stated earlier, insulin is the essential glucose-lowering therapy for the treatment of patients with type 1 diabetes. Therefore, all experimental treatments for type 1 diabetes (and their matching placebos, as applicable) that are not insulin analogues or other insulin receptor ligands should be studied as add-on therapies to insulin.

Preclinical data or knowledge of a particular mechanism of action may indicate that an investigational product has the potential to cause or worsen hypoglycemia, either by binding to insulin receptors or by affecting other aspects of glucose absorption and metabolism. If the investigational product is anticipated to have the potential to lead to hypoglycemia, either directly or through potentiation of insulin effect, the study design should include allowance for insulin dose adjustments to protect trial subjects from hypoglycemia. However, pharmacodynamic interactions with insulin, as well as the need to adjust insulin doses to prevent hypoglycemia, may pose significant challenges for study design, interpretation, and inference of the new drug's efficacy. For example, given the need to titrate insulin to control for glycemia and to guard against hypoglycemia, the blinding of subject and investigator to treatment allocation may not be practical or acceptably safe. Unblinded, controlled trials may be appropriate in some circumstances, particularly for trials incorporating clearly objective endpoints. On the other hand, unblinding can severely limit the interpretability of subjective endpoints (i.e., patient-reported outcomes) that might be incorporated as secondary assessments of efficacy.

In phase 1 and phase 2 trials of products intended to prevent or delay the progression of type 1 diabetes, sponsors are encouraged to conduct randomized, placebo-controlled studies, while investigating early pharmacodynamic markers of effect as well as the safety of the tested product.

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3. *Type 2 Diabetes Mellitus*

Efficacy and safety of new products for the treatment of type 2 diabetes can be evaluated in placebo-controlled monotherapy trials, placebo-controlled add-on therapy trials, and active-controlled trials. Given the progressive nature of type 2 diabetes and the requirement for multiple drug therapy, the clinical development program should involve evaluation of the investigational drug as monotherapy and in combination with many other approved antidiabetic drugs.

In the past, oral agents (i.e., sulfonylureas) to treat type 2 diabetes were approved largely on the basis of placebo-controlled trials with no underlying pharmacological therapy, in which all randomized subjects received only counseling for appropriate diet and an exercise program in addition to the product being tested. As medical care for diabetes has evolved, it may now be difficult to find patients who are appropriate candidates for purely placebo-controlled trials because a large proportion of those diagnosed with diabetes are receiving early pharmacological treatment. Considerations of withdrawal of existing therapy to enroll patients in a placebo-controlled trial of a new agent as initial monotherapy should include informed consent, severity and duration of disease, presence of diabetic comorbidities, and dose of the existing drug therapy. In addition, strict escape or withdrawal criteria for loss of glycemic control should be explicit in the study protocol.

The discontinuation of effective treatment for the purposes of making a patient eligible for inclusion in a placebo-controlled trial of significant duration (e.g., longer than 6 months) raises ethical issues, although placebo-controlled trials of 6 months or less in duration may be appropriate, provided that the protocol contains strict escape or rescue criteria related to hyperglycemia and poor glycemic control. In such trials, the number of patients meeting the escape criteria can be assessed as a measure of efficacy. In any case, we recognize that both placebo-controlled (with or without background therapy) and active-controlled studies can provide the essential safety and efficacy data to support approval.

a. *Studies of a test agent as monotherapy*

Many patients with type 2 diabetes who are potential candidates for studies of new therapeutic agents are likely being treated with one or more antidiabetic medications. Development of a new investigational product to support its indication as monotherapy in type 2 diabetes can be undertaken in subjects who are drug-naïve and whose diabetes is reasonably well controlled with diet and exercise. These subjects can participate in placebo- and dose-controlled studies for up to 24 weeks, provided that they continue to remain in reasonable metabolic control for the duration of the studies (see below for an example of escape or rescue criteria). Likewise, subjects on low doses of a single antidiabetic medication who are under reasonable glycemic control can discontinue their medications under strict glycemic supervision to participate in placebo-controlled studies of an agent to be used as monotherapy.

There also should be a reasonable expectation that placebo dropouts caused by further loss of glycemic control will be limited, thus enabling controlled assessments of both efficacy and safety.

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For either phase 2 or phase 3 studies, regardless of HbA1c at entry, subjects whose hyperglycemia persists or worsens beyond prespecified thresholds should be appropriately monitored and treated throughout the study. In developing these escape or rescue criteria, it is useful to consider that even for drugs that show therapeutic effects only after a matter of weeks (e.g., thiazolidinediones/PPAR agonists), most responders experience a reduction in fasting blood glucose of greater than 20 mg/dL (1.1 mmol/L) by 6 weeks. For agents that lower postprandial rather than fasting glucose levels, a clinically meaningful reduction in HbA1c (e.g., 0.3 percentage units) also usually is evident by 6 weeks. The following are examples of rescue criteria based on thresholds for FPG or HbA1c:

- FPG greater than 270 mg/dL (15 mmol/L) from baseline to Week 6
- FPG greater than 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
- FPG greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 percent from Week 12 to Week 24

For agents that lower postprandial rather than fasting glucose levels, the sponsor is encouraged to enforce specific rescue criteria based on thresholds of unacceptable postprandial glucose encountered during the first 12 weeks of the study and unacceptable HbA1c encountered thereafter.

Even if the escape criteria related to poor glycemic control result in early discontinuation of a substantial proportion of participating subjects, the trial may still be interpretable, at least from the standpoint of efficacy. (For more details, see section V.G., Important Statistical Considerations.) The rate of meeting withdrawal criteria also can provide an assessment of efficacy using a time-to-event analysis if events are collected or responder analysis based on a binary outcome of treatment success or failure. Subjects meeting glycemic rescue criteria ideally should remain in the study even after receiving the additional or alternative therapy to allow for the assessment of safety of the investigational drug or biologic.

Phase 2 or phase 3 studies investigating the efficacy of a new product as monotherapy in subjects already on active therapy for their diabetes can be more problematic. The majority of these subjects will probably experience significant worsening of glycemic control when their medications for diabetes are discontinued. These subjects require a washout period with careful monitoring of glucose. An unknown, and likely high, proportion of subjects simply will either not qualify for studies because of loss of control before randomization or will discontinue because of worsening glycemia in the initial weeks of treatment with poorly effective doses of the investigational drug or with placebo. The washout period should take into account the pharmacokinetic properties of the existing treatment (e.g., 5 half-lives) and the fact that HbA1c reflects mean glycemic control over 2 to 3 months. The length of treatment with the test agent before endpoint ascertainment should account for the duration of the pharmacodynamic effects of previous treatments and the expected timing of a pharmacodynamic effect (e.g., plasma glucose, HbA1c) of the test agent.

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A difference between active drug and placebo (or between two active treatments such as a lower and higher dose of the test agent) in the proportion of subjects meeting criteria for glycemic rescue therapy can be used as a measure of efficacy.

b. Studies of new agents on a background of existing therapy

For subjects taking two or more antidiabetic agents to control glycemia, a potential approach in phase 2 or phase 3 can be a randomized study in which the investigational product or matching placebo is substituted for one of the drugs being taken. Sponsors can conduct extensive dose titration and dose exploration in phase 2 studies of this type, typically 12 to 16 weeks in duration.

For phase 3 studies of investigational agents as add-on therapy, the typical design is not that of substituting the investigational agent for an existing medication, but rather to add the investigational agent to the existing therapy. Typically, these studies are designed as placebo-controlled superiority or active-controlled noninferiority trials. In these studies, patients inadequately controlled on optimal or near-optimal doses of approved therapies should be randomized to one of several doses of the investigational agent or to placebo as add-on to the existing medications (or, in the case of active-controlled trials, to a therapy previously approved for such add-on use). Subjects should be on optimal or near-optimal doses of approved therapies for two reasons: 1) most practicing physicians titrate the dose of one therapeutic agent before considering addition of another antidiabetic agent to improve glycemic control; and 2) this approach allows for more rigorous assessment of the investigational product's efficacy by avoiding a confounding effect of any upward dose titration of the approved medication during the trial.

Another design less commonly used in studies directed at assessing efficacy is the randomized withdrawal. For example, all subjects can be treated with the test agent either as monotherapy or in addition to existing therapy. After a treatment period sufficient to reach pharmacodynamic steady state, subjects can be randomized, in double-blind fashion, either to continue test therapy or to switch to placebo for an additional period (e.g., 12 to 16 weeks). Subjects whose glycemic control deteriorates to the point of meeting escape criteria and requiring additional therapy may create a bias in the assessment of efficacy if the efficacy endpoint is defined as change of HbA1c from randomization to the study endpoint. The primary endpoint for the withdrawal design should be the time to therapeutic failure if event times are collected or, if not, the proportion of HbA1c treatment failures in each treatment group.

B. Study Assessments and Endpoints

1. General Considerations

Throughout development of new molecular entities, particularly within novel classes of therapeutic products, thorough safety evaluations are critical even in the early phase clinical studies. These early studies should be designed with conservative approaches to testing, initially in smaller numbers of subjects, with single doses, and with appropriate safety monitoring not only for glycemia-related parameters, but also for potential hazards identified based on

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preclinical or in vitro study results or on known effects seen with other members of the drug class (if available).

a. Pharmacokinetics

In general, pharmacokinetic parameters of noninsulin therapeutics should be evaluated in phase 1 studies. These studies can be performed in healthy volunteers to determine the basic pharmacokinetic parameters (e.g., absolute bioavailability, area under the curve (AUC), C_{\max} , T_{\max} , $T_{1/2}$). Additionally, pharmacokinetic studies also may be appropriate in the intended patient population. We recommend that exposure-response data be obtained during the phase 2 dose-finding studies. (See the guidance for industry *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.)

In patients with diabetes, the high prevalence of altered glomerular filtration rates, delayed or deficient gastrointestinal transit and absorption, and the potential for interactions with commonly used medications usually dictate the need for the evaluation of the pharmacokinetics of new agents in the target population, beyond investigations in healthy volunteers. It is important to evaluate the in vivo and in vitro mechanisms of drug absorption and disposition. This information will provide the basis for the design of the drug interaction studies addressing the class effects of oral antidiabetic drugs (e.g., addressing the induction potential of CYP enzymes by thiazolidinediones, CYP2C-based interactions with sulfonylureas, and interactions with renal tubular secretion of metformin). We also recommend interaction studies with drugs that have a narrow therapeutic index and with drugs likely to be co-administered in the diabetic population. (See the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* for details.)⁹

Effects of food on pharmacokinetics should be evaluated in the development of therapeutic products that are intended to be administered orally in temporal proximity to meals (e.g., agents designed to exert effects on glycemia peri- or postprandially, such as meglitinides). Because patients with diabetes may be a particularly sensitive population in terms of polypharmacy and underlying, often subclinical, cardiac disease, we also encourage sponsors to address the effect of the drug on the QT interval by conducting a thorough QT study.¹⁰

b. Pharmacodynamic endpoints and biomarkers

Products whose pharmacodynamics, by design, are restricted to effects on postprandial glucose (e.g., meglitinides) should be tested in dose-finding, proof-of-principle, short-term, oral glucose challenge studies. However, such demonstrations of pharmacodynamic activity are not sufficient evidence of efficacy for new drug application (NDA) approval,¹¹ because the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently

⁹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

¹⁰ See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

¹¹ See 21 CFR part 314 for regulations regarding NDAs.

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strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy. Such products should be shown to be safe and effective in improving overall glycemic control based on reduction in HbA1c. That said, description in labeling of the effects of the agent on excursions in postprandial serum glucose concentrations, thereby effecting reductions in overall glycemic exposure (as manifest by reductions in HbA1c), may be warranted in some cases to provide physicians with an understanding of the mechanism of action of the agent and its implication for method of use.

Glycated endogenous proteins with turnover rates faster than hemoglobin, such as fructosamine, can be used as preliminary indicators of a product's effects on integrated glycemic exposures in early phase studies of limited duration. Demonstration of reductions in HbA1c, with a concomitant meaningful decrease in mean daily insulin requirements in relevant patients, is desirable but not necessary for the preliminary inference of efficacy from these early studies. Changes in FPG, plasma glucose level after a standard meal, plasma glucose level after oral administration of 75 g of glucose, average blood glucose (mean of seven home measurements obtained before and after each meal and at bedtime), and fructosamine can be used as primary measures of efficacy in phase 2 studies. They also can be used as secondary, supportive measures of efficacy in phase 3 studies.

c. Efficacy endpoints

For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control. Superiority or noninferiority hypotheses may be appropriate depending on the trial design. Refer to section V.G., Important Statistical Considerations, for a discussion of issues related to noninferiority trials and choice of noninferiority margins as they relate to studies in diabetes. Also see the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

d. Effects on markers of insulin resistance and diabetes comorbidities

Treatment-associated reduction in endogenous hyperinsulinemia (in type 2 diabetes) or improvement in insulin sensitivity are arguably salutary health effects, but do not alone provide sufficient support of a new agent for approval purposes. Effects of antidiabetic agents on blood pressure and serum lipids are of obvious importance and can be described in labeling with disclaimers commensurate with the limitations of the trials regarding extrapolation of findings to conclusions about ultimate drug effects (i.e., on mortality or irreversible morbidity).

e. Effect of weight loss on diabetes

In recent years, the FDA has recommended to sponsors of weight loss products seeking an indication for the treatment of type 2 diabetes that they should demonstrate that the product's effect on glycemic control is independent of weight loss. The FDA has reconsidered the necessity of this recommendation. The FDA's current thinking is that a sponsor can gain approval for the treatment of type 2 diabetes for a drug or biologic whose principal mechanism

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of action appears to be weight loss by showing a clinically meaningful and statistically significant improvement in glycemia.

The development program to support a diabetes indication for these products should be comparable to the development programs used for antidiabetic products not intended for weight loss. For example, the product would need to be studied in subjects with a wide range of body mass indices (from lean to obese), different duration of diabetes (new onset to long-standing), and under different conditions of use (monotherapy and combination therapy). Sponsors interested in the development of weight loss products for the treatment of type 2 diabetes should discuss their plans with the Division of Metabolism and Endocrinology Products.

2. Insulins

In the case of a new insulin with perhaps unique pharmacokinetic characteristics dictating a specific method of use (i.e., dosing interval, timing relative to meals), efficacy can be assumed based on pharmacodynamic (e.g., clamp) studies. However, studies of clinical safety and efficacy usually will be necessary to demonstrate that the method of use leads to effective diabetes management and that the treatment is not associated with undue hypoglycemia (e.g., relative to an approved insulin and standard regimen). (See Appendix B for a discussion on hypoglycemia). These studies should be directed at achieving actual reductions in glycemia (as opposed to simple maintenance of pretrial levels of control) from baseline to end of study. Test and comparator groups should be treated to similar goals. Similar degrees of glycemic control (test noninferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.

a. Insulin mixes

When seeking approval of a new formulation of premixed short- and long-acting insulins, the sponsor should establish the distinctiveness and usefulness of the premixed products compared to each individual insulin component. We recommend that the premixed product's pharmacokinetic and pharmacodynamic profiles have a target difference of at least 20 percent from each of its single components (e.g., NPH and regular/rapid insulin) and also from each adjacent product within its product line. Such differences can be established by the maximum concentrations (C_{\max}) and the various partial AUCs (e.g., $AUC_{0-4 \text{ hr}}$ and $AUC_{4-12 \text{ hr}}$) from insulin plasma exposure versus time profiles. From a pharmacodynamic perspective, the maximum glucose infusion rate (GIR) and the various partial AUCs (e.g., $AUC_{\text{GIR}0-4 \text{ hr}}$ and $AUC_{\text{GIR}4-12 \text{ hr}}$) from glucose infusion rate versus time profiles can be used. In addition, the bioavailability of the new premixed product should remain comparable to the total bioavailability of the short-acting insulin product.

b. Insulin use in pumps (continuous subcutaneous insulin infusion)

Endpoints to be used in the development of insulins for use in pumps should include ascertainment of compatibility between the insulin or analogue and the pump and infusion sets. Likewise, the stability, sterility, and appearance of insulin under laboratory conditions simulating

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the conditions and stresses of actual use should be assessed. Assuming the use of approved pumps and approved insulins, clinical studies *per se* are not usually necessary for approval of the use of a particular insulin in a pump. However, glycemic control may need to be evaluated in a short-term clinical study for novel delivery systems. To clarify expectations for development and approval, additional discussion is encouraged between the FDA (including the Office of Combination Products) and sponsors of particular insulin pumps or insulins.¹²

c. New insulin analogues or insulin receptor binding agonists

In the development of new insulin analogues or insulin receptor binding agonists, sponsors should address the following three fundamental issues in randomized, controlled trials:

1. The risk of hypoglycemia under conditions of use ultimately recommended in labeling, relative to approved insulin products and regimens. In this regard, both test and control groups should achieve improved and similar glucose control as assessed by HbA1c.
2. Pharmacokinetic variability should be evaluated, according to injection site, thickness of fat layer, and other parameters known to affect absorption, distribution, metabolism, and excretion characteristics. Additionally, pharmacodynamic characteristics should be carefully studied to direct dosing interval (for long-acting products) and timing of dosing relative to meals (for short-acting products). Assessment of insulin receptor binding (affinity and dissociation rates), receptor autophosphorylation, phosphorylation of signaling elements and promotion of mitogenesis may add important data to the characterization of new insulin analogues.
3. As a complex biological protein, insulin has the potential to be immunogenic. Adequate assays should be developed that measure antibodies to the test product before the submission of an application. Antibody titers, the timing of their detection and disappearance (if applicable), and correlation with pharmacological effects should be ascertained. The potential for any of the antibodies to neutralize the effects of a new insulin should be assessed, particularly in the presence of high titers of antibodies, and in the presence of allergic reactions or suspicion of immune-complex deposition, or apparent loss of clinical effectiveness.

d. Inhaled insulins

Investigations of insulin delivered by inhalation should include preclinical safety, pulmonary safety, pharmacokinetics, pharmacodynamics, dose proportionality, and hypoglycemic risk. The extent of preclinical studies needed depend, in part, on the novelty of the formulation (e.g., what excipients are used) for the inhaled route. Typically, the minimum preclinical program should be comprised of two 14-day inhalation studies focusing on the histopathology of the respiratory tract, followed by a 6-month bridging study in the most appropriate species. The pharmacokinetics (including bioavailability), pharmacodynamics, and hypoglycemic risk of

¹² It should be noted that proposed labeling may affect the design of trials using a particular insulin with a particular pump.

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inhaled insulin in humans should be compared to that of subcutaneously administered insulin. Intrasubject pharmacokinetic variability should be evaluated.

We encourage sponsors of inhaled insulin products to enroll at least some patients with underlying pulmonary disease, such as chronic obstructive pulmonary disease and asthma, to assess not only effects of inhaled insulin on their pulmonary function, but also the effects of their disease on insulin kinetics. Cigarette smoking affects inhaled insulin bioavailability, and airway status may lead to alterations in drug delivery to the absorption site. Therefore, sponsors should investigate the potential effect of cigarette smoking and inhalational drugs for pulmonary disease on the efficacy and safety of the inhaled insulin product, including assessments of the effects on insulin pharmacokinetic and pharmacodynamic endpoints and the rates and timing of hypoglycemia.

Sponsors developing inhaled insulin products should evaluate the pulmonary safety of these inhaled insulin products (including excipients). Safety assessments should include pulmonary function as measured by the full battery of pulmonary function tests, including spirometry, lung volumes, and diffusion capacity. Serial pulmonary function tests should be performed and the long-term effects of the inhaled insulin product on pulmonary function should be established. Additional safety assessments include high resolution computed tomography of the chest at baseline and on treatment. Because of the potential effects of diabetes mellitus on the pulmonary system, a comparator group is recommended for these safety assessments. In addition, assessment of anti-insulin antibody responses is essential in the overall safety assessment of the inhaled insulins, because the inhaled route may lead to a different propensity toward immune responses. Pre-use storage and in-use handling conditions during these studies should be designed to mimic actual use of the products. Accuracy of use and dosing should be assessed and documented.

3. Noninsulin Products

A reduction in insulin dose is not sufficient stand-alone evidence of efficacy for approval or labeling of a noninsulin product. In addition to showing a meaningful reduction in the insulin dose, the drug should be shown to independently reduce HbA1c, or at least show that no increase in HbA1c accompanies the insulin reduction. In this context, the elimination of the need for insulin entirely in patients with type 1 diabetes or simplification of the insulin regimen while maintaining or improving glycemia (i.e., optimum control with a nonintensive insulin regimen resulting in reduced hypoglycemic risks) is considered clinically meaningful.

Novel approaches to the treatment of type 2 diabetes, such as the use of gastrointestinal neuropeptides or products that inhibit degradation of these peptides, have been shown to have effects beyond the control of insulin secretion and insulin action, such as rate of gastric emptying, food intake, and glucose counterregulation. Nonetheless, the recommended endpoints for approval of such products specifically for the treatment of diabetes will be the same as the traditional approaches used in the development of currently approved insulin secretagogues or insulin sensitizers (i.e., change from baseline in HbA1c).

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Products intended for the treatment of diabetes can be developed for use as monotherapy and for use in combination therapy regimens with other drug classes with different mechanisms of action.

A fixed-dose combination (FDC) of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of two currently approved and marketed drugs, and will be labeled for the same indications and patient populations as the separately approved therapies, and the safety and efficacy of these drugs have been established in co-administration, a full factorial efficacy trial may not be necessary to demonstrate the contribution of each FDC component to the claimed effects. In this setting, pharmacokinetic data defining any drug-drug interactions between the components generally should be sufficient. There are exceptions to this approach, such as situations where there are potential safety concerns with the co-administration of the two components. In addition, we recommend nonclinical toxicity studies for certain FDC products, even when the components are previously marketed drugs or biologics. For details, see the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

4. Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus

Studies of products aimed at the prevention of type 1 diabetes in high-risk subjects, or at preservation of beta-cell function in recent-onset type 1 diabetes with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as the following:

- Fasting and postprandial glucose and glycemic excursion
- Frequency and severity of hypoglycemic events
- Fasting and stimulated C-peptide levels
- Daily insulin requirements in the subjects with diabetes, expressed in international units (IU) per kilogram of body weight

These studies also should evaluate the variations in serum or plasma levels of immune markers, such as anti-insulin, antiglutamic acid decarboxylase 65 and 67, ICA512, and IA-2 beta antibodies. Other markers of cellular immune response (T-cell subpopulations, cytokines) also can be used. In phase 2 studies for the prevention of type 1 diabetes, genotyping and assessments of specific populations of pathogenetically relevant T-cells are encouraged. In particular, the correlation between genotypes and immunoreactive T-cell subpopulations, biomarkers related to glycemic control, and response to treatment may lead to more successful phase 3 studies.

Phase 2 and phase 3 studies of immunosuppressive products or immunomodulators for the prevention of type 1 diabetes also should evaluate their effects on general immune responses, including T-cell proliferation in response to conventional antigens, immunoglobulin subclasses, and titers of antibodies in response to primary antigens and recall responses. Depending on the known or suspected mechanism of action, as well as findings from previous clinical and nonclinical studies, other endpoints should be considered in the overall safety evaluation. These

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assessments should be conducted in patients with diabetes, and not borrow substantially from other patient populations, such as populations with neoplasia or post-transplant patients treated concomitantly with other immunosuppressants.

Phase 3 studies of investigational products intended for the prevention of type 1 diabetes mellitus in high-risk individuals typically will designate a delay in the diagnosis of type 1 diabetes as the criterion for defining efficacy. An appropriate endpoint to support efficacy can be the proportion of subjects in the treatment groups who develop frank diabetes after a prespecified period of time (the period being at least 1 year) compared across treatment groups.

Preservation of beta-cell function in patients recently diagnosed with type 1 diabetes is being actively pursued by the pharmaceutical industry and in government and academic collaborations. We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical benefits in patients who achieve better glucose control, in terms of delaying the chronic complications of diabetes. Similarly, we acknowledge that patients who had greater preservation of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline were more likely to have lower HbA1c with fewer hypoglycemic events over time.

Phase 3 development of investigational products intended to preserve endogenous beta-cell function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study endpoint (typically 1 or 2 years) in both treatment groups, and demonstrate maintenance of C-peptide or an attenuation in the rate of decline compared to the control group. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm. A favorable effect on these endpoints should be balanced against the risks of the particular intervention being tested. Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and whether they experience a lower frequency of hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes.

As with most prevention claims, we generally will accept fewer risks for treatments intended to prevent type 1 diabetes compared with treatments that preserve endogenous beta-cell function in patients already diagnosed with type 1 diabetes.¹³ This distinction is made because some individuals exposed to prevention strategies have no chance for benefit, as they are not inexorably destined to develop diabetes. Therefore, some patients (who presumably cannot be pre-identified) would be subject to the risks of the treatment with no hope of benefit.

5. Prevention of Type 2 Diabetes Mellitus

In phase 3 studies for products intended to prevent the development of type 2 diabetes in high-risk individuals (such as individuals with impaired glucose tolerance, impaired fasting glucose, or with a history of gestational diabetes), potential endpoints supporting approval include delay in type 2 diabetes diagnosis or reduction in the proportion of patients diagnosed with type 2

¹³ See 21 CFR 56.111(a)(1)(i) regarding the unnecessary exposure of subjects to risk.

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diabetes by ADA criteria, relative to placebo. These study designs should include a follow-up (washout) period to assess whether the tested agent truly delays progression to diabetes or only masks diabetes during the treatment period. Such studies will likely be of substantial duration (years) and size. The FDA cannot *a priori* define the magnitude of a clinically meaningful effect size.

For prevention studies of drugs with a pharmacological action of improving glycemic parameters (e.g., approved treatments used in the prevention setting), improvement in clinical parameters beyond those that would be expected from glucose lowering alone should be demonstrated, since the forestalling of a biochemical diagnosis of frank diabetes from the prediabetic state may not itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such supportive evidence can include a demonstration of a durable delay in the onset of type 2 diabetes after the prevention therapy is stopped, or can show that the delay in progression to type 2 diabetes mellitus is accompanied by other indicators of clinical benefit (e.g., delay or lessening in microvascular or macrovascular complications). That said, the more modest the treatment effect, the higher the standard for safety and the more restricted (e.g., to subjects at highest risk for near-term conversion to frank type 2 diabetes) the indicated target population.

C. Metabolic Syndrome

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. A host of therapies now exist to address individual or multiple components of the syndrome (e.g., lipid-altering agents, antihypertensives, insulin sensitizers). A therapeutic product intended to treat the metabolic syndrome ideally should normalize or improve all components of the syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality. As mentioned in the Introduction section, a full discussion of this syndrome is beyond the scope of this guidance.

D. Study Population Considerations

In general, premarket study populations should be representative of the population for which the product, once approved or licensed, is intended. Two specific considerations with regard to study populations are listed below.

1. Pediatric Populations

Under the Pediatric Research Equity Act (PREA), section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 355c), as amended by the Food and Drug Administration Amendments Act of 2007 (Public Law No. 110-85), sponsors must study a product in all relevant pediatric populations when submitting an application under section 505 of the Act (21 U.S.C. § 355) or section 351 of the Public Health Service Act (42 U.S.C. § 282) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. However, the PREA requirements may be waived or deferred in certain

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circumstances. Although a detailed discussion of how sponsors may comply with the PREA requirements is beyond the scope of this guidance, several relevant points are addressed below.

In the case of new molecular entities, particularly for new classes of therapeutic products with novel mechanisms of action, the early studies should enroll adult subjects only, reserving pediatric exposure until the metabolism, pharmacodynamics, and safety of the agent are reasonably well-defined. The same precaution can be applied to already approved agents with known toxicities in nondiabetic populations, such as immunosuppressive or immune modulatory products. Because many of the general aspects of the clinical pharmacology and safety profiles of an approved therapeutic are better understood, it may be appropriate to dose pediatric patients earlier in the development programs of approved versus unapproved investigational products.

In the initial development of insulins and other agents with potential to cause hypoglycemia, we recommend that subjects with particularly labile glucose control and a substantial history of recent hypoglycemia be excluded. Because of the high representation of children and adolescents in the population with type 1 diabetes, patients in these demographic subsets usually should be included early in the clinical development of treatments for type 1 diabetes. However, it is not appropriate to study all products for type 1 diabetes in children before approval. For example, inhaled insulins, which represent simply an alternate route of administration for a well-established active ingredient, should be developed for adult use initially because of uncertainties in the safety of new inhalation dosage forms. After additional safety data are developed, these products can be studied in children, including during the postmarketing period. In such cases, the initial approved labeling should specifically address dosing and administration in adults. Labeling for pediatric use can be developed and approved after additional studies are conducted in pediatric patients.

Given the increasing representation of children and adolescents with type 2 diabetes, studies of therapeutic products intended for the treatment of type 2 diabetes should at some point include patients younger than 18 years of age, assuming no obvious contraindications to such use (e.g., hypothetical effects on growth and development based on mechanism of action).

Sponsors may contact the review division for further information with regard to meeting the PREA requirements.

2. Other Study Populations

Type 2 diabetes occurs more frequently in Latino, African American, and Native American patients relative to patients of northern European descent. Therefore, attempts should be made to enroll representative numbers of individuals from these ethnic groups during the clinical development program, particularly during the phase 3 trials. Attention also should be paid to considerations in geriatric patients, including decreased renal function, autonomic dysfunction, poor glucose-counterregulatory response, hypoglycemia unawareness, and potentially dangerous interactions with other commonly used drugs. It is desirable to determine whether demographic, genetic, metabolic (e.g., C-peptide, body mass index, previous antidiabetic therapy), or other factors predict responses to a new antidiabetic agent, predispose patients to certain toxicities, or otherwise affect tolerability and compliance.

E. Sample Size and Study Duration

The ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* recommends a total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions. However, exposures exceeding these recommendations should be used for products developed for the treatment of type 2 diabetes, given the large and growing size of the population with type 2 diabetes and the increasing complexity of treatment regimens. At the time of submission of the marketing application (either a biologics license application (BLA) or an NDA) for products intended for the treatment of type 2 diabetes mellitus, we recommend that phase 3 trial data be available for at least 2,500 subjects exposed to the investigational product with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed to the investigational product for 18 months or more.

These investigational products should be tested as monotherapy and in combination with antidiabetic medications with which they likely will be co-administered in clinical practice. As treatment of type 2 diabetes mellitus frequently requires combination therapy, overall exposures and length of duration should be weighted more in trials evaluating the investigational product with other antidiabetic medications. The guidance for industry *Premarketing Risk Assessment* also anticipates situations where larger numbers of exposures for longer periods might be needed, including for diseases where many sufficiently safe alternative treatments already exist or for a preventive treatment. Therefore, we encourage long-term extensions of 6- to 12-month controlled trials and anticipate that the safety information relevant for approval will be provided at the initial submission of an application.

Development of products intended to preserve beta-cell mass and function in type 1 or type 2 diabetes can be considered in enriched populations, where genetic or immunologic markers predicting the natural history of the disease exist. Testing the investigational product in high-risk populations enriched for such markers enhances power to detect an effect of the intervention (if one exists), as compared to testing the product in the general diabetic population. Even in enriched populations, pivotal studies may still need to be relatively long (e.g., 2 or more years) to show a meaningful effect, given the natural history of the decline in beta-cell function in the target populations and also recognizing the need for long-term safety information.

For all new development programs for drugs to treat diabetes, phase 3 studies should be sized to allow meaningful evaluation of the consistency of effects across subgroups based on sex, age, ethnic background, duration and severity of the disease (e.g., based on categories of HbA1c at baseline), interactions with other likely concomitant medications as combination therapies, and other relevant factors specific to the product and indication sought. Randomized treatment groups should be well balanced for these factors, and to fully ensure balanced assignment, randomization stratified for a limited number of factors may be desirable, with particular emphasis on those baseline variables hypothesized to affect either safety or efficacy.

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Most patients taking products intended to treat diabetes are titrated to achieve a particular effect on serum or plasma glucose or on HbA1c. The primary efficacy parameter should be assessed substantially after the end of the titration period (e.g., 3 months) to better reflect the steady-state effect of the dose regimens studied.

Regardless of the choice of control used in phase 3 studies, the duration of the controlled phase in an efficacy trial is an important issue. In studies of recently approved products that lasted more than 1 year, sponsors have typically conducted a randomized, controlled study lasting at least 6 months, followed by an extension phase lasting 6 months or longer. Sponsors should weigh the advantages and disadvantages when deciding between a controlled and uncontrolled extension phase, and should ensure that the chosen design will provide interpretable long-term data.

Although uncontrolled extensions still allow for an expanded safety database (both in numbers exposed and duration of treatment), interpretability of both efficacy and safety data in an uncontrolled study period is limited by lack of a control group.

Since diabetic populations are prone to certain morbidities (such as cardiovascular disease and renal dysfunction), only longer term comparative safety data would allow for an assessment of the relative rates of these common, but important morbidities in subjects assigned to the investigational agent versus the control. Studies lasting longer than 1 year that employ an appropriate active comparator with adjudication of safety endpoints of interest by an endpoint committee blinded to treatment are strongly encouraged and may be needed if preclinical or phase 2 or phase 3 studies reveal a safety signal. Longer term controlled data also allow for better assessments of the comparative durability of effects on glycemia. Such studies, however, may have high rates of dropouts; therefore, treatment algorithms for maintenance of adequate glycemic control should be considered in the study design.

Of note, all drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. The FDA currently bases approval of these drugs and biologics on HbA1c. We recognize that reducing long-term macrovascular complications in patients with diabetes should be an important goal of disease management. Although a recommendation to demonstrate macrovascular risk reduction premarketing may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy, sponsors should conduct large outcomes trials before submission of marketing applications for drugs in development that show nonclinical or clinical evidence of increasing macrovascular risk. Therapies that have not demonstrated a deleterious effect on cardiovascular outcome during extensive premarketing evaluation may need further post-approval assessment for their effects on long-term macrovascular disease. Interpretation of data resulting from such studies may be complicated by the need to identify conclusively the effect of a single drug within a multidrug regimen that usually is part of an adequate treatment for a complex, progressive condition such as type 2 diabetes and its associated comorbidities.

Phase 3 studies with a 6-month, placebo-controlled phase can be extended into a rigorously controlled, randomized, double-blind active-controlled phase that employs double-dummy agents.

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Before submitting a marketing application, assessment of the immunogenic potential of therapeutic proteins, including insulins and insulin analogues, and of monoclonal antibodies, should be performed over a period of at least 6 to 12 months in study subjects reasonably representative of the intended population. If adverse events characteristic of allergic or immunologic reactions are identified, we may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of a marketing application or as a postmarketing commitment, based on the overall analysis of the risks and benefits of the product. The appropriate timing of additional studies in these circumstances can be discussed with the FDA at a pre-BLA meeting, pre-NDA meeting, or other similar advice meeting.

A licensed monoclonal antibody used only in allogeneic transplantation, where patients are immunosuppressed through multiple modalities, should be newly evaluated for immunogenic potential in the diabetic or high-risk prediabetic population.

F. Premarketing Safety Evaluation

The safety evaluation of a new drug is, in the end, directed by the findings of preclinical investigations, by concerns arising based on the mechanism of action of the drug, by known toxicities of agents with a similar chemical structure or mechanism of action, and by the findings of previous clinical trials. In other words, ultimately, the safety evaluation is an iterative process based on prior experience.

Additionally, new antidiabetic agents, used alone or in combination with approved agents, should be assessed for their tendency to cause or augment hypoglycemia, an event that is part of diabetes management. Acceptable hypoglycemic risk, although not defined in absolute terms, usually is risk that is comparable to existing therapies, to which the new drug is directly compared, when both drugs are used in trials in which subjects are treated to identical glycemic goals with comparable glycemic outcomes (e.g., ADA guidelines). Furthermore, patients with diabetes often use multiple medications, not only to control glycemia, but also to address cardiovascular disease risk factors, such as hypertension and hyperlipidemia, and microvascular and neuropathic complications of diabetes. Interactions between the new investigational product and these other medications can result in adverse events that should be considered, documented, and reported. Finally, worsening of comorbid conditions other than diabetes should be ascertained, reported, and analyzed in comparison to the rates of similar adverse events in the control group.

Findings of specific safety signals with a product or related product (whether cardiovascular or otherwise) during any development phase should be investigated further in controlled studies enriched with the population at risk for the signal. The timing of this investigation (pre-approval or post-approval) depends on the strength and nature of the signal and whether the treatment offers a major advance over existing therapies.

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For general issues related to risk assessment, pharmacovigilance, and risk minimization plans, refer to the following guidances:¹⁴

- Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*
- Guidance for industry *Development and Use of Risk Minimization Action Plans*
- Guidance for industry *Premarketing Risk Assessment*
- ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and addendum
- ICH guidance for industry *E2E Pharmacovigilance Planning*

G. Important Statistical Considerations

Standard statistical considerations apply to programs for drugs or biologics intended to treat diabetes. However, the following discussion highlights a few specific areas that are important to consider specifically for these therapeutic products.

1. Sample Size

Sample size calculations for superiority trials with HbA1c change from baseline as the primary endpoint should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes should represent clinically meaningful differences.

Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5 percent and at least 80 percent power. Because the calculations depend on the noninferiority margin, the sponsor should provide a rationale for the choice of margin and should be guided by the concept that this margin should not represent a clinically meaningful loss of efficacy relative to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.

2. Preventing Missing Data from Subjects Who Prematurely Withdraw from Treatment

We encourage sponsors to obtain HbA1c measurements in all subjects, including those who withdraw prematurely or receive rescue medication because of poor glycemic control, near the calendar date at which they were scheduled to complete the trial. Complete data collection can facilitate the desired goal of a true intent-to-treat analysis (i.e., the analysis of all randomized subjects) and also serve as a measure of good clinical trial conduct.

¹⁴ See <http://www.fda.gov/cder/guidance/index.htm>.

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3. Analysis Methods

We recommend that the analysis of HbA1c change from baseline adjust for differences between groups in HbA1c at baseline (e.g., ANCOVA with baseline HbA1c as a covariate in the model). Factors in addition to treatment can be included in the model as appropriate, particularly variables with substantial correlation with the outcome and independence from the treatment, and variables used to stratify the randomization.

Although every reasonable attempt should be made to obtain complete HbA1c data on all subjects, dropouts are often unavoidable in diabetes clinical trials. The resulting missing data problems do not have a single general analytical solution. Statistical analysis using last observation carried forward (LOCF) is easy to apply and transparent in the context of diabetes trials. Assuming an effective investigational therapy, it is often the case that more placebo patients will drop out early because of a lack of efficacy, and as such, LOCF will tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug's effect. The primary method the sponsor chooses for handling incomplete data should be robust to the expected missing data structure and the time-course of HbA1c changes, and whose results can be supported by alternative analyses. We also suggest that additional analyses be conducted in studies with missing data from patients who receive rescue medication for lack of adequate glycemic control. These sensitivity analyses should take account of the effects of rescue medication on the outcome.

The full analysis set as described in ICH E9 should be the primary analysis population for both superiority and noninferiority analyses. Supporting analyses in one or more subsets of the full analysis set also can be conducted and are encouraged in noninferiority analyses.

Analyses of data from studies using withdrawal designs depend on the type of primary endpoint. Survival analysis methods should be used if therapeutic failure times are collected. If the endpoint is therapeutic success or failure, categorical methods should be used.

If statistical significance is achieved on the primary endpoint, secondary assessments of efficacy can be considered. Type 1 error should be controlled across all clinically relevant secondary efficacy endpoints that may be intended for product labeling to provide statistical support for their inclusion in the label.

The sponsor should report least-square mean treatment differences and associated 95 percent confidence intervals from the primary statistical model for all continuous efficacy endpoints.

Rates of hypoglycemia should be compared statistically between groups. If count data are analyzed, the sponsor should use robust statistical methods that take account of the dependence of events within individual patients.

4. Graphical Methods

Graphical methods showing treatment effects over time for study completers should be presented. Additional graphical presentations of the data to illustrate the effect of the drug are

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1063 encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for*
1064 *Human Prescription Drug and Biological Products — Content and Format.*
1065

**APPENDIX A:
PRECLINICAL CONSIDERATIONS FOR PEROXISOME
PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS**

Because of the effects of PPAR agonists on glucose and lipid metabolism, many compounds are being developed for the treatment of type 2 diabetes and/or dyslipidemia which activate PPAR α , PPAR γ , PPAR α and γ (dual agonist), or PPAR α , γ , and δ (pan agonist).

Recommendations for the Duration of Chronic Toxicology Studies

The ICH guidance regarding the duration of chronic toxicity studies in rodents and nonrodents has been adopted,¹⁵ and for the nonrodent chronic toxicity study, a 9-month duration generally is appropriate for supporting chronic human use. However, since the no observed adverse effect levels for some of the toxicities associated with PPAR agonists can be adequately defined only after chronic administration, a 1-year study in nonrodents is recommended for drugs in the PPAR class.

Because of the prevalence of positive carcinogenicity findings with PPAR agonists, 2-year carcinogenicity evaluations in mice and rats are recommended. Since heart weight increases of 25 percent or greater after 13-week treatment with PPAR agonists have been predictive of excess cardiac mortality with longer-term chronic dosing (greater than or equal to 12 months) in all animal models, a dose that results in 20 to 25 percent increases in heart weight is considered to define the maximum tolerated dose for use in the 2-year carcinogenicity study for agonists with gamma activity.

Recommendations for the preclinical evaluation of PPAR-related toxicities are as follows:

- **Cardiac Effects.** The effects on the heart should be characterized by reviewing electrocardiograms, clinical chemistry, and cardiac histopathology in rats and nonrodents. QT prolongation potential should be thoroughly evaluated in multiple dose nonrodent toxicity studies. For compounds with PPAR alpha or delta agonist activity, biomarkers of direct cardiac toxicity such as Troponin I and T should be monitored in animal studies.

Additional evaluations are recommended as follows:

- Correlation of heart weights with thickness of ventricular free wall and ventricular septum in chronic toxicology studies in rats and nonrodents.
- Morphometric measurements of ventricular myocardial hypertrophy in nonrodents.
- Presence of karyomegaly in myocardium of ventricles.
- Pattern and distribution of myocardial fibrosis.
- Characterization of myocardial inflammatory infiltrates.
- Determination of composition of serous effusions.
- Presence of fatty changes detected by stained heart tissue. The sections can be stained with Sudan IV or Oil Red-O.

¹⁵ See the ICH guidance for industry *S4 Duration of Chronic Toxicology Testing in Animals (Rodent and Nonrodent Toxicity Testing)*.

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- Characterization in animals and humans of the potential for plasma volume expansion.
- **Hepatic Effects.** The cause of any liver enlargement observed should be determined (peroxisome proliferation, mitochondrial proliferation/swelling). Liver tissues should be stained to detect the presence of fatty changes. The sections can be stained with Sudan IV or Oil Red-O. Liver enzyme levels and biochemical markers of peroxisome proliferation (Acyl CoA and CYP 4A) should be analyzed in rodents and nonrodents.
- **Bone Marrow Effects.** Bone marrow smears from femur and sternum should be quantified to assess for effects on cellularity.
- **Renal Effects.** Drug-related increases in urothelial tumors have been observed in rodent carcinogenicity studies with PPAR agonists. If such tumors are observed, mechanistic studies (e.g., urinalysis assessing crystalluria, urine pH, urinary electrolytes) are recommended.
- **Muscle Toxicity.** Skeletal and/or cardiac muscle degeneration have been commonly observed for agonists with PPAR alpha or PPAR delta activity. Creatine kinase and troponin evaluations should be performed in preclinical studies for these subtypes. Histopathological evaluations of skeletal muscle should include multiple sites to evaluate effects on both type I and type II muscle (e.g., diaphragm, gastrocnemius, soleus, intercostals muscles).
- **Other Known Toxicities.** Thymic and lymphoid atrophy, reproductive organ toxicity, adipose proliferation, and infiltration are toxicities commonly associated with the administration of PPAR agonists in preclinical studies. Preclinical study designs should include adequate assessments for these potential toxicities.
- **Electron Microscopy.** Electron microscopy evaluations should be conducted on established target organs for PPAR agonists (liver and heart mandatory) and on other compound specific target tissues, as identified (e.g., renal proximal tubules, skeletal muscle).

APPENDIX B: HYPOGLYCEMIA

Severe episodes of hypoglycemia are often encountered when patients implement a program of intense glycemic control. These adverse occurrences are often the limiting factor in achieving improvements in metabolic control and reductions in HbA1c. There are often substantial differences in the interpretation and reporting of the severity of hypoglycemic episodes among investigators, studies, and clinical programs because of the diversity of the definitions used in clinical studies. To help in the interpretation of this important safety attribute of a new diabetes treatment that may cause hypoglycemia, we recommend standardization of definitions in individual protocols and across protocols within the development program. One recommended approach for such standardization is to use classifications of severity from well-accepted sources, such as the ADA.

The ADA Workgroup on Hypoglycemia classifies hypoglycemia as follows (Diabetes Care, 2005, 28: 1245):

- **Severe hypoglycemia.** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- **Documented symptomatic hypoglycemia.** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).
- **Asymptomatic hypoglycemia.** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70 mg/dL (3.6 to 3.9 mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.
- **Probable symptomatic hypoglycemia.** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.

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- **Relative hypoglycemia.** An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L). This classification reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels greater than 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and, therefore, may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

At a minimum, hypoglycemic events should be reported in each of the first three classifications: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.

Currently, there is no standardized convention for reporting the frequency of hypoglycemia in clinical studies. The ADA Workgroup recommends that both the proportion (percentage) of subjects affected and the event rates (e.g., episodes per subject-year or 100 subject-years) for each of the classifications of hypoglycemic events be reported. These data provide complementary information. In addition, we anticipate that the distribution of subjects having a specific number of hypoglycemic events will be reported (see also section V.G., Important Statistical Considerations). For the hypoglycemic episodes, sponsors should include information on potential precipitants (e.g., missed meal, exercise) and patterns (e.g., timing of the event during the course of the day or night).

**APPENDIX C:
CURRENTLY AVAILABLE DRUG TREATMENTS**

A. Insulin Products

A variety of recombinant human insulins and insulin analogues are available and these products serve as the primary basis for treating the glucose metabolic defects in type 1 diabetes. Insulin and its analogues also have an important role in the treatment of type 2 diabetes, particularly as the disease progresses. These products are used in different combinations according to the pharmacokinetic profile of each insulin type, and some are available in premixed combinations of different proportions of short- and long-acting agents. These insulins also can be used in conjunction with oral agents (described below) to achieve control of blood glucose. There has been tremendous interest and some success in developing noninjectable insulins (e.g., inhaled insulin). However, current development of these products has been aimed at supplementing or replacing short-acting insulin only and would not represent a full alternative to injectable insulin and its analogues.

B. Oral Agents for Type 2 Diabetes

The first oral products for the treatment of diabetes mellitus were the sulfonylureas, which are long-acting insulin secretagogues. The meglitinides constitute another class of insulin secretagogues that are taken with meals and have short-term effects, primarily on the postprandial elevations of plasma glucose. Metformin exerts its effect on endogenous hepatic glucose production. PPAR agonists enhance insulin sensitivity. Alpha glucosidase inhibitors prevent intestinal glucose absorption and have primary effects on the excursion of postprandial glucose.

C. Newer Classes of Therapeutic Products

More recently, an analogue of human amylin, pramlintide, was approved for the treatment of type 1 or type 2 diabetic patients as an adjunct to mealtime short-acting or rapid-acting insulin. Amylin, a neuroendocrine hormone that is co-secreted with insulin from pancreatic beta cells, slows intestinal carbohydrate absorption through decreased gastric emptying and suppresses hepatic gluconeogenesis by inhibiting glucagon secretion postprandially. Additionally, exenatide, a glucagon-like peptide 1 (GLP-1) analogue (belonging to the new class of incretin mimetics) has been approved for type 2 diabetes, in combination with other oral antidiabetic agents. In response to nutrients in the lumen of the gut, GLP-1 is secreted from the intestinal L cells. Similar to amylin, GLP-1 decreases gastric emptying and glucagon secretion. In addition, GLP-1 stimulates insulin secretion. Because the effects of GLP-1 are glucose-dependent, GLP-1 mediates glucose homeostasis without causing hypoglycemia. Both pramlintide and exenatide are injectables.

There is a newer class of oral drugs known as dipeptidyl peptidase 4 (DPP4) inhibitors that has been the focus of intense development. DPP4 is a serine protease responsible for the rapid metabolism of endogenous GLP-1. By inhibiting this enzyme, DPP4 inhibitors prevent the rapid catabolism of endogenous GLP-1, thereby potentiating the incretin effect of GLP-1.

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**December 2008
Clinical/Medical**

Guidance for Industry

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Guidance for Industry¹

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.² Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

In March 2008, the FDA issued the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.³ Concerns related to cardiovascular risk will be addressed in the final version of that guidance. In the meantime, we are issuing this final guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs. We will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For discussion of general issues of clinical trial design or statistical analysis, see the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although several drug treatments currently are available, we recognize the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs and therapeutic biologics).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure). Both type 1 and type 2 diabetes have a heritable basis. Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.⁴ Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.⁵

There are also compelling data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control. Glycemic control in these studies has been based on changes in HbA1c. This endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. Therefore, reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus. However, diabetes mellitus is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. Although this excess cardiovascular risk is present in both type 1 and type 2 diabetes, the

⁴ See N Engl J Med, 1993, 329:977-986.

⁵ See Diabetes, 2006, 55:3556-3565.

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absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. For type 2 diabetes, the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings. After considering the discussion at this meeting as well as other available data and information,⁶ we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- 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.
- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.
- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

⁶ See Lancet, 1998, 352:837-853 and 854-865.

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controlled trials, and to preserve the study level randomized comparison but include, when possible in the meta-analysis, important identifiers of study differences or other factors (e.g., dose, duration of exposure, add-on drugs). It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.

- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.
- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.⁷
- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary.

⁷ See the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901. This section will become section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A).

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- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings.

Sponsors are encouraged to contact the division to discuss specific issues that arise during the development of a new antidiabetic therapy to treat type 2 diabetes.