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APPLICATION NUMBER:

22-350

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Submission Code N000

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Reviewer Name Naomi Lowy, MD
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Established Name Saxagliptin
(Proposed) Trade Name Onglyza
Therapeutic Class Dipeptidyl-peptidase IV inhibitor
Applicant Bristol-Myers Squibb Company

Priority Designation S

Formulation Oral tablet
Dosing Regimen 5 mg daily
2.5 mg daily (moderate, severe, or
end-stage renal impairment)
Indication Treatment of type 2 diabetes
Intended Population Adults

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1 Recommendations/Risk Benefit Assessment

Saxagliptin (ONGLYZA™) is an orally-active, reversible dipeptidyl peptidase 4 (DPP4) inhibitor that has been developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The Sponsor is seeking three indications: as monotherapy, in combination therapy with metformin, a sulfonylurea (SU), or a thiazolidinedione (TZD), when the single agent alone does not provide adequate glycemic control, and as initial combination with metformin, when treatment with dual saxagliptin and metformin is appropriate. The proposed usual clinical dose is 5 mg once daily, with a recommended dose of 2.5 mg once daily in subjects with moderate or severe renal impairment, and end-stage renal disease requiring hemodialysis.

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval of saxagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (although the Sponsor requested individual indications for various treatment settings, the Division has streamlined the indications for anti-diabetic drugs). The Sponsor has demonstrated modest efficacy along with an acceptable safety profile. However, the following recommendations also apply:

- A dose reduction to 2.5 mg when saxagliptin is used with CYP3A4/5 inhibitors, such as ketoconazole. C
- As of the completion of this Review, recommendations regarding the use of saxagliptin in women of childbearing potential have not been finalized. This issue arose out of a pre-clinical study done to support the fixed dose combination of saxagliptin and metformin in which certain fetal abnormalities were seen (discussed in Section 4.3). Final decisions regarding this issue will be addressed in a pharmacology/toxicology memorandum and the Cross Discipline Team Leader (CDTL) memorandum.

1.2 Risk Benefit Assessment

Although there are a number of available medical therapies available for type 2 diabetes mellitus (Section 2.2), the progressive nature of the disease demands new therapies that can safely and effectively be used either alone or added on to the current armamentarium of drugs. Given that the Sponsor has demonstrated efficacy in monotherapy and combination therapy settings, saxagliptin can play a useful role in type 2 diabetes treatment.

The Sponsor conducted six Phase 3 studies (referred to as “Core Phase 3 studies” in this Review) that were randomized, double-blind, and placebo-controlled (two monotherapy studies, three add-on combination studies to metformin, sulfonylurea, and a thiazolidinedione, and one initial combination with metformin study). In the Phase 3 program, the Sponsor chose to study 3 doses

of saxagliptin (2.5, 5, and 10 mg), which allowed for a more comprehensive safety and efficacy evaluation.

The Sponsor has demonstrated modest efficacy with saxagliptin, demonstrated with the following reductions in HbA1c relative to placebo: 0.52-0.56% as monotherapy, 0.72-0.83% when used as add-on to metformin, 0.6-0.7% when used as add-on to sulfonylurea, and 0.4-0.6% when used as add-on to thiazolidinedione. Saxagliptin was also studied as initial combination therapy with metformin, and this combination reduced HbA1c 0.5% relative to metformin alone. With this modest efficacy, saxagliptin offers the benefit of an oral formulation, convenient once-daily dosing independent of food intake, weight neutrality, low risk for hypoglycemia, and further HbA1c lowering in diabetic patients who are already receiving maximum doses of other antihyperglycemic therapies.

The Sponsor has also demonstrated a favorable safety profile of saxagliptin. This is based on an exposure database of 3422 subjects exposed to saxagliptin in Phase 2 and 3 studies, including 1269 subjects exposed to the proposed clinical dose of saxagliptin (5 mg). This exposure also reflects 1937 subjects exposed to saxagliptin for ≥ 52 weeks. Although non-clinical data for saxagliptin were concerning for necrotic skin lesions in monkeys at concentrations X-fold higher than clinical exposures with the 5 mg daily dose, this was not observed in the clinical program, which tested doses up to 100 mg in 44 subjects for 6 weeks and up to 400 mg in 6 subjects for 2 weeks. Additional safety concerns that arose in the clinical program included saxagliptin-related decreases in lymphocyte and platelet counts (see Section 7). These safety issues, which do not appear to have clinical relevance, have been adequately addressed by the Sponsor, and do not appear to outweigh the demonstrated benefit of saxagliptin.

Although I agree with the Sponsor's proposed clinical dose of 5 mg daily as well as the recommended dose of 2.5 mg daily in subjects with moderate, severe, and end-stage renal disease, the Sponsor has not adequately addressed dose adjustment concerning certain drug-drug interactions (see Section 4.4). Saxagliptin is predominantly metabolized in the liver by CYP3A4/5. In the Clinical Pharmacology review of this drug, the effect of strong CYP3A inhibitors and inducers on saxagliptin concentrations emerged as an important issue. Drug-drug interaction (DDI) studies identified a more than 2-fold increase in AUC of saxagliptin in the presence of ketoconazole. In one *in vivo* DDI study, the combination resulted in a majority of subjects experiencing a decline in lymphocyte count accompanied by pyrexia and chills. Given these findings, a dose reduction to 2.5 mg is recommended when patients are prescribed concomitant CYP3A4/5 inhibitors.

The Clinical Pharmacology review determined no need for higher doses of saxagliptin when taken with CYP3A4/5 inducers.

Limitations of the saxagliptin clinical development program include low enrollment of blacks and the elderly. Therefore despite subgroup analyses which did not identify major differences between subgroups, interpretation of these results is limited.

1.3 Recommendations for Postmarketing Risk Management Activities

As discussed later in this Review, cardiovascular safety was the subject of an Endocrinologic and Metabolic Advisory Committee (EMDAC) meeting held on April 1, 2009. With the implementation of the committee's recommendations, and as per the Food and Drug Administration Amendments Act of 2007 (FDAAA), the Division will require a post-marketing cardiovascular safety trial, particularly in a higher risk population. See Sections 7 and 9.3 for details regarding the advisory committee.

The timelines for the cardiovascular postmarketing requirement are still under discussion but the final dates will be included in the Approval letter.

1.4 Recommendations for other Post Marketing Study Commitments

Saxagliptin has been studied in subjects ≥ 18 years old. Under the Pediatric Research Equity Act (PREA), saxagliptin must be studied in the pediatric population unless there are reasons to waive this requirement. The Sponsor requested a waiver for pediatric studies in children less than 10 years of age, and this waiver has been granted because there are too few children with the disease to study. FDA has previously granted a waiver for pediatric studies in children less than 10 years of age for another DPP4 inhibitor. The Division agrees with the Sponsor's proposal to study subjects 10 years of age up to but excluding 18 years with type 2 diabetes mellitus. The Sponsor proposes to conduct a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin monotherapy in pediatric patients with type 2 diabetes. This would include a 16-week, randomized, double-blind phase, followed by a 36-week extension phase of continued double-blind treatment (for group randomized to saxagliptin) or a cross-over to double-blind metformin (for group randomized to placebo). The Sponsor also proposes a pre-randomization pharmacokinetic sub-study. The details of pediatric testing will be finalized when complete protocols are submitted. The sponsor's pediatric plans were discussed with the Pediatric Review Committee, which agreed with the cut points for the waiver and deferral and the overall general approach to assessing efficacy and safety of saxagliptin in children.

2 Introduction and Regulatory Background

2.1 Product Information

Product Description

Saxagliptin, (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate, is an orally active, selective, reversible inhibitor of dipeptidyl peptidase IV (DPP4) intended to improve glycemic control for patients with type 2 diabetes mellitus in adults.

Established Name

Saxagliptin (also identified as BMS-477118)

Proposed Trade Name

The proposed trade name for saxagliptin is Onglyza®. The Division of Medication Error Prevention and Analysis found this proposed name acceptable.

Chemical Class

Saxagliptin is a New Molecular Entity (NME).

Pharmacologic Class

Saxagliptin, a selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor, belongs to a newer class of oral anti-diabetic agents termed “incretin enhancers”.

Saxagliptin is the fourth DPP-IV inhibitor to undergo FDA review as a New Drug Application (NDA). This includes one that is currently under review in the Division.

Applicant’s Proposed Indication

The Sponsor proposes saxagliptin as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus:

- As monotherapy
- In combination with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU) when the single agent alone, with diet and exercise, does not provide adequate glycemic control; and
- As initial combination therapy with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate.

Applicant’s Proposed Dosing Regimen

The proposed clinical dose is 5 mg once daily. In subjects with moderate or severe renal impairment, and end-stage renal disease requiring hemodialysis, the proposed dose is 2.5 mg once daily.

Saxagliptin is a CYP3A4/5 substrate, and the effect of strong CYP3A inhibitors and inducers on saxagliptin concentrations was analyzed by Clinical Pharmacology. A dosage reduction to 2.5 mg is recommended when patients will be prescribed CYP3A4/5 inhibitors, such as ketoconazole. The Sponsor’s proposed label does not recommend a dose adjustment while taking concomitant CYP3A4/5 inhibitors. On the other hand, the use of CYP3A4/5 inducers with saxagliptin does not require a dosage increase of saxagliptin.

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Saxagliptin (Onglyza™)

Applicant's Proposed Age Groups

Adults (≥ 18 years of age).

2.2 Tables of Currently Available Treatments for Proposed Indications

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 Saxagliptin (Onglyza™)

Table 2.1. Currently approved pharmacologic therapies for type 2 diabetes mellitus

Therapy	Example	Primary mechanism of action	Expected decrease in HbA1c (%)	Adverse Effects	Effect on weight
Sulfonylureas	Glyburide	Increases insulin secretion	1.0-2.0	Hypoglycemia	Weight gain
Glitinides	Repaglinide	Increases insulin secretion	1.0-2.0	Hypoglycemia	Weight gain
Biguanides	Metformin	Decreases hepatic glucose output	1.0-2.0	Gastrointestinal symptoms	Weight neutral
Alpha-glucosidase inhibitors	Acarbose	Delays gastrointestinal absorption of carbohydrates	0.5-1.0	Flatulence	Weight neutral
Thiazolidinediones	Pioglitazone	Increases insulin sensitivity	0.5-1.0	Edema	Weight gain
Insulin	Lispro	Increases insulin levels	1.5-2.5	Hypoglycemia, weight gain	Weight gain
Amylin analogues	Pramlintide	Slows gastric emptying	0.5-1.0	Gastrointestinal symptoms	Weight loss
GLP-1 Analogues	Exenatide	Stimulates glucose-dependent insulin release	0.5-1.0	Gastrointestinal symptoms	Weight loss
DPP-4 Inhibitors	Sitagliptin	Stimulates glucose-dependent insulin release	0.8	Uncommon	Weight neutral
Bile Acid Sequestrants	Colesevelam	Binds bile acids	1.0	Gastrointestinal symptoms	Weight neutral
Dopamine receptor agonists	Cycloset	Unknown	0.5	Gastrointestinal	Weight neutral

Source: Adapted from AACE Diabetes Mellitus Guidelines (2007) and Nathan D. (2002)

2.3 Availability of Proposed Active Ingredient in the United States

Saxagliptin is a new molecular entity and has not yet been marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Several DPP-IV inhibitors in development, including saxagliptin, produce dose- and duration-dependent necrotic skin lesions in Cynomolgus monkeys. The FDA therefore has required that each DPP-IV inhibitor undergo testing in a three-month monkey toxicity study.

Vildagliptin, another DPP-IV inhibitor in development, has been associated with liver test elevations.

Finally, there have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin (Januvia™). These include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

End of Phase 2 meeting (July 27, 2005)

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

Reviewer comments: The Sponsor performed two monotherapy studies (CV181011 and CV181038), for which results of both are included in the NDA. Rather than incorporating dose titration into an extension portion of one monotherapy study, the Sponsor incorporated dose titration of saxagliptin into the short-term (ST) and long-term (LT) periods of CV181038 (see below for an explanation of the ST and LT period). No other Phase 3 study incorporated dose titration. The 1 mg dose was not used in the Phase 2b/3 program. Doses of saxagliptin were restricted to 2.5, 5, and 10 mg.

FDA: For patients requiring rescue, the last value before rescue therapy should be used in the statistical analyses.

Reviewer comments: The primary efficacy endpoint of each Core Phase 3 Study was the change in HbA1c from baseline to Week 24 for saxagliptin compared with placebo or active comparator. If a subject was rescued, the last pre-rescue post-baseline measurement prior to Week 24 was used. If no Week 24 assessment was available, Last Observation Carried Forward (LOCF) methodology was used.

Pre-NDA meeting (November 14, 2007)

FDA: The Division acknowledged that although there are several secondary variables based on efficacy, some are considered exploratory and may not be appropriate in labeling.

Reviewer comment: In the proposed labeling, the Sponsor has included claims of

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FDA: The Division expressed concern that the Sponsor planned to submit a lot of data in the 4 month update report (SUR), particularly for the add-on to sulfonylurea (SU) and thiazolidinedione (TZD) studies. The projected one-year exposures to saxagliptin for these studies at the time of NDA filing appeared low and would then double at the 4 month update. The Division requested sample sizes of at least 200 saxagliptin-treated subjects at 50 weeks at the time of NDA filing for the monotherapy and for the each of the combination therapy settings. Based on these concerns, on December 7, 2007, the Sponsor submitted a revised proposal for saxagliptin patient exposures at the time of NDA submission and at the time of the safety update. The revised proposal is summarized here:

	Overall	Mono (011, 038, 039, 041)	Combo Metformin (014, 039)	Combo SU (040)	Combo TZD (013)
≥24 Weeks					
N at NDA	2617	813	1029	459	316
N at 4 Month	2617	813	1029	459	316
SUR	Δ=0	Δ=0	Δ=0	Δ=0	Δ=0
≥50 Weeks					
N at NDA	1338	335	527	306 ^a	170 ^b
N at 4 Month	2180	652	853	410	265
SUR	Δ=842	Δ=317	Δ=326	Δ=104	Δ=95

^aversus 185 in plan proposed at pre-NDA meeting on November 14, 2007

^bversus 150 in plan proposed at pre-NDA meeting on November 14, 2007

The Division agreed to the revised proposal. Exposures as submitted in the NDA and the SUR are presented in Table 2.2 below. These met and exceeded the numbers proposed by the Sponsor.

Table 2.2. Extent of Exposure for ST + LT Periods: All Phase 2/3 Studies 120-Day Safety Update					
N= Number of Treated Subjects					
Mean in Weeks (SD)					
Subject-Years					
	2.5 mg	5 mg	10 mg	All Saxa	Control
Pooled Monotherapy	N=247	N=252	N=98	N=597	N=169
(CV181011, CV181038)	59.2 (35.34)	63.5 (37.00)	84.4 (45.48)	65.1 (38.81)	64.6 (39.32)
	280.02	306.46	158.57	745.06	209.37
Add-on Combination	N=192	N=191	N=181	N=564	N=179
+ Met	91.7 (42.08)	87.9 (44.17)	95.2 (40.42)	91.5 (42.31)	75.9 (43.73)
(CV181014)	337.35	321.79	330.38	989.52	260.39
+ SU	N=248	N=253	N/A	N=501	N=267
(CV181040)	63.0 (20.71)	63.6 (20.98)		63.3 (20.83)	60.0 (22.38)
	299.52	308.45		607.97	307.06
+ TZD	N=195	N=186	N/A	N=381	N=184
(CV181013)	58.7 (21.73)	54.6 (24.61)		56.7 (23.25)	52.4 (24.67)
	219.39	194.46		413.86	307.06
Initial Combination	N/A	N=320	N=323	N=978	N=328
+ Met		50.1 (19.83)	51.0 (20.29)	49.3 (20.32)	48.0 (21.72)
(CV181039)		307.51	315.88	924.01	301.47
			N=335		
			(monotherapy)		
			46.8 (20.63)		
			300.62		

Source: 120-Day Safety Update, Table 2.1.1B

FDA: The Division requested that the Sponsor use 2 methods to define Hy's Law—one definition should require alkaline phosphatase $<2\times$ ULN; the second definition should not have an alkaline phosphatase requirement. The Division also requested that the Sponsor provide, in easily accessible format, the actual liver test values for patients with ALT or AST $> 3\times$ ULN and actual serum creatinine for patients with outlier values for serum creatinine.

Reviewer comments: The Sponsor did this.

FDA: The Division requested that when reporting the most common adverse events (AEs), the Sponsor should use a cut-off value of $\geq 2\%$ instead of the proposed \sim cut point.

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Reviewer comment: The Sponsor reported all common AEs using a cut-off value of $\geq 2\%$.

2.6 Other Relevant Background Information

The Incretin Effect

The incretin effect is defined by a significantly greater insulin stimulatory effect evoked after an oral glucose load than that evoked from an intravenous infusion when plasma glucose concentrations are matched.ⁱ The majority of this phenomenon is thought to primarily be due to oral glucose stimulating the release of glucose-dependent insulinotropic peptide (GIP) and glucagon like peptide-1 (GLP-1), both termed incretins. Patients with type 2 diabetes have a significant reduction of this effect. GLP-1 concentrations are reduced in patients with type 2 diabetes in response to a meal, and GIP concentrations are either normal or increased.

GIP and GLP-1

Within minutes after food ingestion, GIP is secreted from the K-cells located in the proximal region of the jejunum. Although it stimulates insulin release in response to hyperglycemia, GIP does not inhibit glucagon secretion and has no effect on gastric emptying. GLP-1 is stored in the L-cells of the ileum and colon. It is also released with food ingestion. Its effects on postprandial glucose concentration arise from the following mechanisms: enhancing insulin secretion, suppressing postprandial glucagon secretion in a glucose-dependent manner, and slowing the rate of gastric emptying. Patients with type 2 diabetes have an impaired insulin response to GIP but a preserved insulin response to GLP-1. Therefore, GLP-1 has been the focus of incretin therapeutics in type 2 diabetes.

DPP-IV

In plasma, both GIP and GLP-1 undergo proteolytic cleavage by DPP-IV, a serine protease distributed throughout the body and located on the cell surfaces of multiple organs, including kidneys, liver, and intestine.ⁱⁱ It is also expressed on a subset of CD4+ and CD8+ T cells. DPP-IV activity is extremely fast so that the half-lives of GIP and GLP-1 are approximately 7.3 minutes and 1-2 minutes, respectively. The rationale for DPP-IV inhibitor therapy is to block the

action of DPP-IV with a molecule that competes for the binding site on the DPP-IV enzyme. This approach prolongs the circulating time of active endogenous GLP-1 by preventing its cleavage.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor's application was adequately organized. With minor exceptions, information was easily retrievable. Minor information requests to the Sponsor generally received prompt and adequate attention. Narratives for all Serious Adverse Events could not initially be located; however, the Sponsor promptly and thoroughly identified the locations, which were dispersed throughout the initial submission.

Inspections of the Sponsor and certain clinical sites were completed. The studies appear to have been conducted adequately, and the data generated by the clinical sites may be used in support of the respective indication.

3.2 Compliance with Good Clinical Practices

The clinical studies were conducted in accordance with ethical standards. Two issues arose which could have potentially affected data quality:

- 1) In studies CV181038 (monotherapy), CV181039 (initial combination with metformin), and CV181040 (add-on combination to sulfonylurea), glucose in excess of the intended 75 g dose was ingested in a number of oral glucose tolerance tests (OGTTs). Data from these procedures, which affected a total of 382 subjects, were excluded from OGTT-related parameters (including AUCs of insulin, glucagon, and glucose). This error primarily impacted the efficacy results in Study CV181038 by further reducing the sample size in this relatively small study.

Reviewer comment: This error did not impact the primary endpoint of the Core Phase 3 studies. Although a substantial number of subjects were affected by this error, including those in the monotherapy study CV181038, no subject in the monotherapy study CV181011 was affected. It is therefore reasonable to extract results of these secondary endpoints from the unaffected monotherapy study. OGTT results from patients given the correct glucose load in the other trials can be qualitatively compared to the corresponding results from CV181011 to assess for consistency of the findings.

- 2) Due to a government-issued suspension on all export of biological samples from Russia over several weeks, a laboratory in Moscow was designated as an emergency central laboratory for all sites in Russia. This only affected Studies CV181038 and CV181039. For those laboratory parameters used in efficacy analyses, samples were frozen during the suspension and held to be analyzed at the central laboratory at a later date. Any

efficacy laboratory parameter analyzed at the emergency central laboratory was not utilized in the efficacy analyses; only results from samples analyzed at the central laboratory were utilized, as per protocol. This reviewer has requested that the sponsor clarify the number of samples involved and whether freezing and thawing of these affected samples altered reliability of the efficacy results. The sponsor's response is pending at the time this review is being finalized and will be addressed in the Cross Discipline Team Leader memorandum.

Tables 3.1-3.3 summarize the protocol deviations for the monotherapy, add-on combination, and initial combination with metformin studies (Core phase 3 studies). In general, deviations were distributed evenly across treatment groups. One exception was seen in Study CV181038, in the saxagliptin 2.5/5 mg qam dose group, where approximately 11% of subjects did not have their "final dose correct according to titration criteria". This was the only study that incorporated dose titration of saxagliptin in addition to rescue, accounting for this specific deviation.

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 Saxagliptin (Onglyza™)

Table 3.1. Protocol Deviations for ST Period of Monotherapy Studies

	Saxa 2.5 mg N=102	Saxa 5 mg N=106	Saxa 10 mg N=98	Placebo N=95
Study CV181011				
Protocol Deviation				
Non-compliance with study medication during ST	1 (0.98%)	1 (0.94%)	1 (1.02%)	1 (1.05%)
Use of Other Antihyperglycemic medication ≥14 days during double-blind period	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Screening platelet count <145,000 cells/uL	2 (1.96%)	2 (1.89%)	1 (1.02%)	1 (1.05%)
Use of other Antihyperglycemic medication during lead-in and ST	1 (0.98%)	0 (0.00)	3 (3.06%)	1 (1.05%)
Absolute lymphocyte count <1000 at screening	1 (0.98%)	1 (0.94%)	1 (1.02%)	0 (0.00)
Accidental receipt of wrong study medication	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.05%)
Body mass index >40 at screening	1 (0.98%)	0 (0.00)	0 (0.00)	0 (0.00)
Study CV181038				
	Saxa 2.5 mg qam N=74	Saxa 5 mg qam N=74	Saxa 2.5/5 mg qam N=71	Saxa 5 mg qpm N=72
Placebo N=74				
Non-compliance with study medication during ST	3 (4.05%)	1 (1.35%)	1 (1.41%)	1 (1.39%)
Corticosteroid Therapy During Lead-in And Short-term	4 (5.41%)	1 (1.35%)	3 (4.23%)	1 (1.39%)
Final Dose not Correct According to Titration Criteria	0 (0.00)	0 (0.00)	8 (11.27%)	0 (0.00)
Accidental receipt of wrong study medication	0 (0.00)	0 (0.00)	1 (1.41%)	0 (0.00)
Treatment with Potent Systemic Cytochrome CYP3A4 Inhibitors or Inducers During Lead-in and Short-term	1 (1.35%)	1 (1.35%)	1 (1.41%)	1 (1.39%)
Hepatitis at Screening	1 (1.35%)	0 (0.00)	0 (0.00)	1 (1.39%)

Source: Clinical Study Reports, CV181011 and CV181038, Tables 4.3 and S.2.3

Clinical Review
 Naomi Lowy, M.D.
 NDA 22,350 (Submission 000)
 Saxagliptin (Onglyza™)

**Table 3.2. Protocol Deviations for ST Period for Add-on Combination Studies
 Study CV181014**

	Number (%) of Subjects			
	Saxa 2.5 mg + Met N=192	Saxa 5 mg + Met N=191	Saxa 10 mg + Met N=181	Placebo + Met N=179
Non-compliance with study medication during ST	0 (0.00)	2 (1.05%)	2 (1.10%)	3 (1.68%)
Use of Other Antihyperglycemic medication ≥14 days during double-blind period	1 (0.52%)	0 (0.00)	0 (0.00)	1 (0.56%)
Change in Metformin Dose Prior to Screening	7 (3.65%)	4 (2.09%)	2 (1.10%)	5 (2.79%)
Platelet count <145,000 cells/uL	4 (2.08%)	4 (2.09%)	3 (1.66%)	1 (0.56%)
Prior treatment with DPP-IV Inhibitor	3 (1.56%)	1 (0.52%)	1 (0.55%)	2 (1.12%)
Non-compliance with study medication during lead-in	1 (0.52%)	2 (1.05%)	1 (0.55%)	2 (1.12%)
Other Antihyperglycemic Medication during Lead-in and Short-term	1 (0.52%)	0 (0.00)	1 (0.55%)	1 (0.56%)
Antihyperglycemic Medication 8 Weeks Prior to Screening	1 (0.52%)	1 (0.52%)	0 (0.00)	0 (0.00)
C-peptide <1.0 ng/mL at Screening	2 (1.04%)	0 (0.00)	0 (0.00)	0 (0.00)
Significant abnormal liver function: ALT >2.0 x ULN at Screening	0 (0.00)	1 (0.52%)	0 (0.00)	1 (0.56%)
BMI >40 at Screening	1 (0.52%)	0 (0.00)	0 (0.00)	0 (0.00)
Continuation of Subject Despite Thrombocytopenia	1 (0.52%)	0 (0.00)	0 (0.00)	0 (0.00)
Hemoglobin ≤1.0 g/dL (F) or ≤12.0 g/dL (M) at Screening	1 (0.52%)	0 (0.00)	0 (0.00)	0 (0.00)
Significant cardiovascular history	0 (0.00)	1 (0.52%)	0 (0.00)	0 (0.00)
Study CV181040				
	Saxa 2.5 mg + Gly N=248	Saxa 5 mg + Gly N=253	Saxa 10 mg + Gly N=267	
Non-compliance with Glyburide during ST	0 (0.00)	1 (0.40%)	0 (0.00)	
HbA1c <6.8% at Randomization	1 (0.40%)	0 (0.00)	2 (0.75%)	
MFPG or MFVBG or FPG is <130 mg/dL at Randomization	0 (0.00)	1 (0.40%)	0 (0.00)	
Use of Other Antihyperglycemic medication ≥14 days during double-blind period	1 (0.40%)	1 (0.40%)	1 (0.37%)	
Other Sulfonylurea Medication ≥14 Days During Lead-In	1 (0.40%)	1 (0.40%)	3 (1.12%)	

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	Saxa 2.5 mg + TZD N=195	Saxa 5 mg + TZD N=196	Placebo + TZD N=184
Administration of Antihyperglycemic Therapy Prior to Screening	4 (1.61%)	1 (0.40%)	4 (1.50%)
Other Antihyperglycemic Medication during Lead-in and Short-term	2 (0.81%)	2 (0.79%)	4 (1.50%)
Pre-randomization Clinically Significant Lab or ECG Abnormalities Which Would Preclude Randomization	1 (0.40%)	1 (0.40%)	0 (0.00)
Absolute Lymphocyte Count ≤1000 prior to first dose of ST	0 (0.00)	0 (0.00)	1 (0.37%)
Accidental Receipt of Wrong Study Medication During ST	1 (0.40%)	0 (0.00)	0 (0.00)
Platelet count <140,000 cells/uL prior to first dose of ST	0 (0.00)	0 (0.00)	1 (0.37%)
Study CV181013			
<80% or >120% Double-blind Study Medication Compliance During double-blind	0 (0.00)	1 (0.54)	2 (1.09)
<80% or >120% Double-blind Study TZD Compliance During double-blind	3 (1.54)	1 (0.54)	1 (0.54)
Other Antihyperglycemic Medication During Double-blind	0 (0.00)	0 (0.00)	1 (0.54)
Receipt of wrong dose TZD for ≥14 consecutive days during ST	1 (0.51)	3 (1.61)	1 (0.54)
C-peptide <1.0 ng/mL at Screening	0 (0.00)	1 (0.54)	0 (0.00)
Change in TZD dose prior to screening	0 (0.00)	0 (0.00)	2 (1.09)
Non-compliance with study medication during Lean-in	0 (0.00)	2 (1.08)	1 (0.54)
Hemoglobin ≤11.0 g/dL (F) or ≤12.0 g/dL (M) at Screening	0 (0.00)	1 (0.54)	0 (0.00)
Other Antihyperglycemic Medication during Lead-in and Short-term	2 (1.03)	4 (2.15)	7 (3.80)
Wrong dose of TZD therapy during lead-in and ST	1 (0.51)	4 (2.15)	1 (0.54)

Source: *Clinical Study Reports, CV181014, CV181040, and CV181013, Tables 4.3 and S.2.3*

Clinical Review
 Naomi Lowy, M.D.
 NDA 22,350 (Submission 000)
 Saxagliptin (Onglyza™)

Table 3.3. Protocol Deviations for ST Period of Study CV181039

Protocol Deviation	Saxa 5 mg + Met N=320	Saxa 10 mg + Met N=323	Saxa 10 mg N=335	Metformin N=328
Non-compliance with study medication during ST	12 (3.8)	8 (2.5)	16 (4.8)	12 (3.7)
Use of Other Antihyperglycemic medication ≥ 14 days during double-blind period	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)
Absolute lymphocyte count <1000 at screening	2 (0.6)	3 (0.9)	0 (0.0)	0 (0.0)
Accidental receipt of wrong study medication	1 (0.3)	3 (0.9)	4 (1.2)	3 (0.9)
BMI >40.5 at Screening	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
C-peptide <1.0 ng/mL at Screening	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Non-compliance with study medication during lead-in	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Continuation of Subjects despite serum creatinine elevation during ST double-blind period	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Hemoglobin ≤ 1.0 g/dL (F) or ≤ 12.0 g/dL (M) at Screening	0 (0.0)	0 (0.0)		
Hepatitis at Screening	1 (0.3)	1 (0.3)	2 (0.6)	0 (0.0)
Other Antihyperglycemic Medication During Lead-In and ST	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)
Platelet Count <14,000 cells/uL Prior to First Dose of ST	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Significant Cardiovascular History	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Treatment with Potent Systemic Cytochrome CYP3A4 Inhibitors or Inducers During Lead-in and Short-term	6 (1.9)	5 (1.5)	7 (2.1)	2 (0.6)

Source: Clinical Study Report, CV181039, Tables 4.3 and S.2.3

3.3 Financial Disclosures

The Sponsor was unable to collect financial disclosure information from a number of investigators/subinvestigators. There were reviewed completely. With the exception of one Principal Investigator, all missing disclosure information was that of subinvestigators. The majority of the study sites at which these subinvestigators participated enrolled none or few subjects. The one Principal Investigator identified _____ for whom disclosure information was not submitted randomized a total of _____ subjects in Study _____

b(6)

Only two Investigators disclosed potential conflicts of interest:

- 1) _____ reported payments to him or his spouse from the Sponsor which were projected to exceed \$25,000. He was an Investigator in Study _____ and randomized _____ subject (0.22%).
- 2) _____ hold an equity position with the Sponsor in excess of \$50,000. _____ was an Investigator for Studies _____ (randomized _____ subjects, 0.66%), _____ (randomized _____ subjects, 0.3%), and _____ (randomized _____ subject, 0.07%). _____ was a _____ for her _____ Study _____

b(6)

b(6)

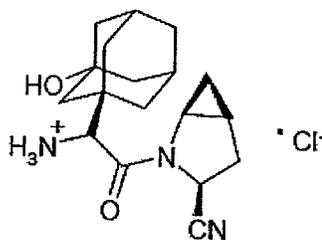
These Investigators randomized a small proportion of overall subjects in the clinical development program. Overall, potential bias from these two Investigators would have minimal, if any, effect on saxagliptin's safety and efficacy conclusions.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Dr. John Hill's CMC Review for full details. All issues identified in during the review have been adequately resolved.

Saxagliptin film-coated tablets (2.5 mg and 5 mg) have been developed for commercialization. The active drug product is the hydrochloride salt form of the drug substance. The structure of this salt form is presented here:



Molecular Formula: $C_{18}H_{25}N_3O_2 \cdot HCl$

Molecular Weight: 351.87

The tablets are manufactured by a _____ The
film-coated tablets do not contain any novel excipients. Saxagliptin drug substance is
manufactured using _____

b(4)

4.2 Clinical Microbiology

Not applicable—saxagliptin is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

See Dr. Fred Alavi's Pharmacology/Toxicology review for full details.

From a cardiovascular perspective, there was no pre-clinical evidence of cardiac toxicities indicative of human risk.

The rat embryofetal study conducted to support the fixed dose combination of saxagliptin and metformin had an unexpected finding of craniorachischisis, incomplete closure of the skull, in two fetuses from a single dam treated with saxagliptin and metformin. Craniorachischisis is a rare and severe form of neural tube defect. Of note, saxagliptin monotherapy is not teratogenic at very high safety margins relative to expected human exposures. There was no metformin arm in this embryofetal study to determine whether the finding is attributable to metformin alone or due to an interaction between metformin and saxagliptin. The final pharmacology/toxicology recommendations are pending regarding labeling of this finding. Please see the pharmacology/toxicology reviews and Cross Discipline Team Leader memorandum for further details.

4.4 Clinical Pharmacology

See Dr. Jayabharathi Vaidyanathan's Clinical Pharmacology review for full details.

The final to-be-marketed tablets are similar to the formulation used in phase 3 trials except for the color and embossing. Saxagliptin molecule contains chiral centers. Chiral conversion was examined and there was no conversion *in vivo*. Saxagliptin has a major metabolite, BMS-510849, which is further discussed below.

A total of 27 Clinical Pharmacology studies were conducted in 673 subjects (620 saxagliptin-exposed). Of these, 583 were healthy subjects (540-saxagliptin-exposed), 32 subjects with renal impairment (all exposed to saxagliptin), and 18 subjects with hepatic impairment (all exposed to saxagliptin), and 40 subjects with type 2 diabetes (all exposed to saxagliptin). There were an additional 23 bioanalytical reports, 17 *in vitro* metabolism/permeability studies, and one protein binding study.

The dose-ranging study (CV181008) was 12 weeks in duration and examined doses in the range of 2.5 mg-40 mg. The detailed Protocol is included in the Appendix, and results are summarized here.

CV181008

This Phase 2b study was a randomized, double-blind, dose-ranging, placebo-controlled parallel group study comparing 5 doses of saxagliptin (2.5, 5, 10, 20, and 40 mg) with placebo (0-40 mg cohort) and comparing a higher dose (100 mg daily) with placebo in treatment-naïve subjects with type 2 DM. The primary efficacy endpoint was to show a positive efficacy trend among the 5 doses of saxagliptin by assessing the change from baseline in HbA1c following 12 weeks of double-blind treatment. Because similar reductions in HbA1c were achieved with all doses of saxagliptin, the test for log linear trend across the treatment groups did not demonstrate a statistically significant ($p=0.9888$) dose-response relationship. However, statistically and clinically significant decreases in HbA1c were seen at all doses of saxagliptin. Specifically, the placebo-subtracted adjusted mean change in HbA1c was: -0.45%, -0.63%, -0.54%, -0.47%, and -0.53% for the 2.5, 5, 10, 20, and 40 mg groups, respectively. For the 100 mg dose (6 weeks treatment), the placebo-subtracted adjusted mean change from baseline to Week 6 was -0.73%.

4.4.1 Mechanism of Action

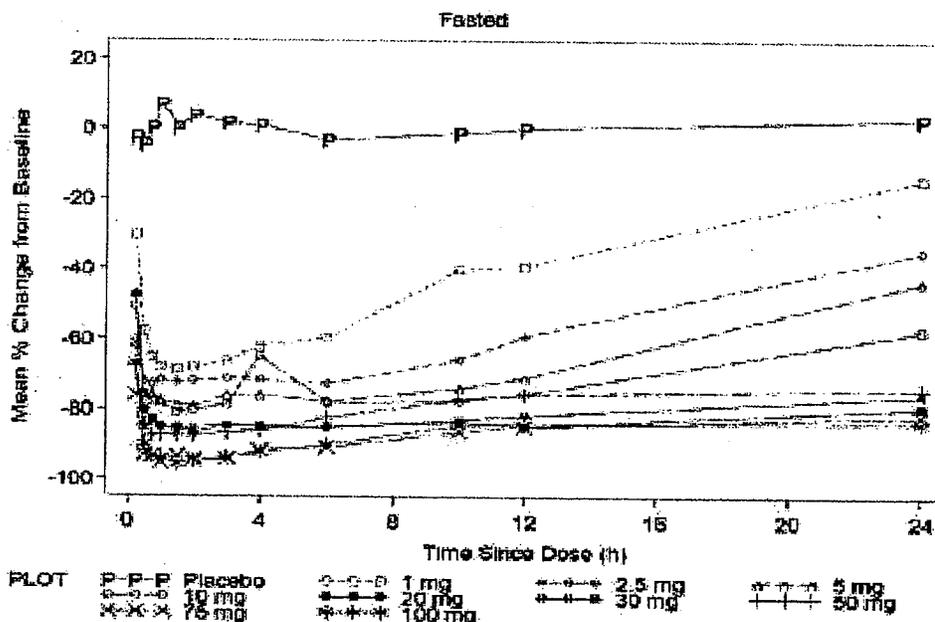
DPP-4 is an enzyme responsible for the inactivation of the incretin hormones, as discussed in Section 2.6. DPP-4 is found in the plasma and as a cell surface enzyme located on vascular endothelium and on epithelial cells in a number of organs. Saxagliptin is an inhibitor of DPP-4, thereby prolonging the life of circulating incretin hormones and improving glucose dependent insulin secretion and reduction of inappropriate glucagon secretion.

4.4.2 Pharmacodynamics

Effect on DPP-4 inhibition

Saxagliptin inhibited plasma DPP-4 activity in a dose-dependent manner. With single dose administration in healthy subjects (Study 001), 73% and 79% maximum inhibition was achieved during the first 0.75-2 hours after administration of saxagliptin doses of 2.5 mg and 5 mg. After 24 hours post-dose, inhibition was 35% and 44%, respectively, for the 2.5 mg and 5 mg doses. This is depicted in Figure 4.1 below.

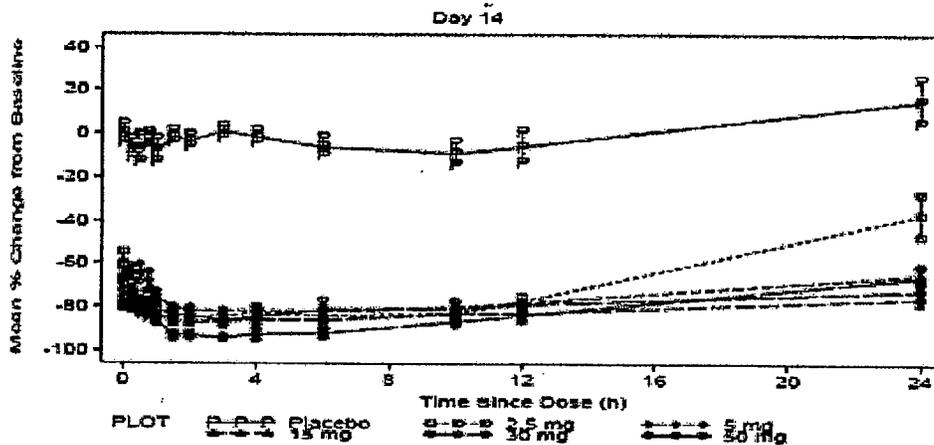
Figure 4.1. Mean Percent Changes from Baseline for Plasma DPP-4 Activity following single oral dose of saxagliptin



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 3

In multiple dose administration in healthy subjects (Study 010), DPP-4 inhibition peaked between 0.75 and 4 hours after dosing on both Days 1 and 14. The DPP-4 inhibition observed appeared to be dose-dependent for doses up to 150 mg. Dosing with saxagliptin at 100, 150, 200, 300, and 400 mg resulted in larger inhibition of plasma DPP-4 activity than dosing with saxagliptin 40 mg. For these doses, plasma DPP-4 activity was inhibited by at least 74% at 24 hours after a single dose and following two weeks of daily dosing. Peak inhibition of DPP-4 activity on Days 1 and 14 occurred 1-2 hours post-dose, coinciding with the T_{max} values for both saxagliptin and BMS-510849, one of its metabolites.

In multiple dose administration in subjects with type 2 diabetes, DPP-4 inhibition was dose-dependent. In subjects receiving saxagliptin, DPP-4 inhibition peaked between 1.5 and 6 hours after dosing. At 24 hours post-dose, there was 37% and 65% inhibition with doses of 2.5 and 5 mg, respectively. The figure below depicts these responses:



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 5

Effect on GLP-1 concentrations

In healthy subjects, saxagliptin appeared to have a non-dose-dependent effect on GLP-1 concentrations, with an increase in mean changes from baseline for postprandial AUC (0-3h) active GLP-1 compared to placebo subjects for all meals. Although dosing with saxagliptin did result in an increase in GLP-1 levels, it did not appear to have a dose-dependent or time-dependent effect on plasma GLP-1 concentrations.

In saxagliptin-treated subjects with type 2 diabetes, there were also non-dose-dependent effects on GLP-1 concentrations. GLP-1 concentrations peaked at an average of 6 hours after dosing. Exceptions included the 2.5 mg and 50 mg dose groups, which were, respectively, observed to have peak GLP-1 concentrations at 45 minutes after dosing on Day 1 and at 1 hour after dosing on Days 1 and 14.

Thorough QT Study in Healthy Volunteers

To confirm that saxagliptin has no effect on QTc interval or heart rate, this randomized, double-blind, four-period, four-treatment, multiple-dose, cross-over study was performed in healthy subjects. Both placebo and positive (moxifloxacin) controls were used.

The FDA Interdisciplinary Review Team for QT studies confirmed that no effect of saxagliptin on QT interval was detected in this study. The largest upper limits of the two-sided 90% CI for the mean difference between saxagliptin (10 and 40 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The overall findings are summarized in Table 4.1.

Table 4.1. The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Saxagliptin (10 mg and 40 mg) and the Largest Lower Bound for Moxifloxacin 400 mg based on QTcF

Treatment	Time, hr.	$\Delta\Delta\text{QTcF}$, ms	90% CI, ms
Saxagliptin 10 mg	4	0.9	-1.6, 3.4
Saxagliptin 40 mg	12	0.7	-2.6, 3.9
Moxifloxacin 400 mg*	4	11.5	8.8, 14.2

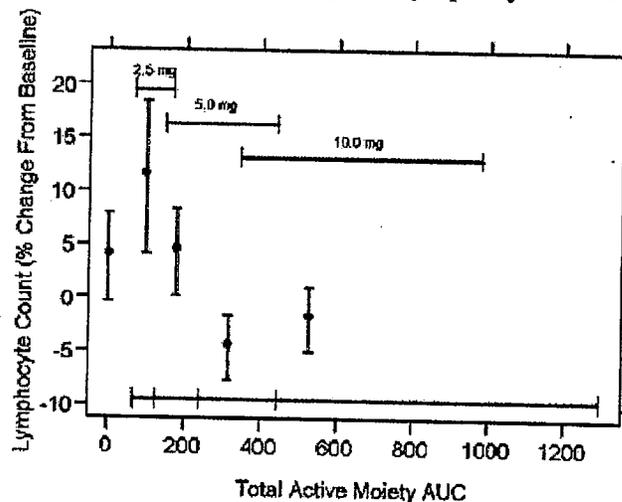
Source: Thorough QT Study Review, FDA Interdisciplinary Review Team for QT Studies, Table 1

Finally, other safety and tolerability issues were explored and analyzed. These include the effect of saxagliptin on lymphocyte count and platelet count. These are also discussed in Section 7.

Lymphocyte count

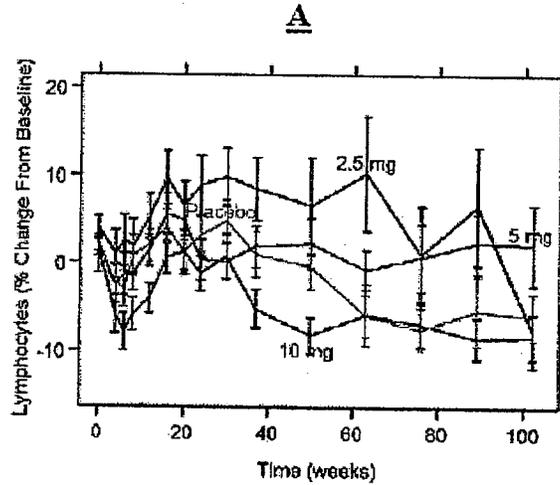
The relationship between lymphocyte count and saxagliptin exposure, derived from the pharmacometric analysis and Study CV181011, is represented in Figure 4.2. The greatest reduction in lymphocyte count (4% at 24 weeks) was observed for saxagliptin exposures of 5 mg or higher. Although a dose-dependent response was not seen, the 10 mg dose was associated with the greatest decrease, an approximately 10% change from baseline (Figure 4.3).

Figure 4.2. Exposure-Response Relationship for Lymphocyte Count



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 11
 Mean percent change from baseline in lymphocyte count at week 24 for each quartile of exposure (AUC) are plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% CIs for the AUC for total active moiety for each dose are plotted as lines indicating the range of response for the expected distribution of AUC values within each dose. The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.

Figure 4.3. Time course of lymphocyte response by dose

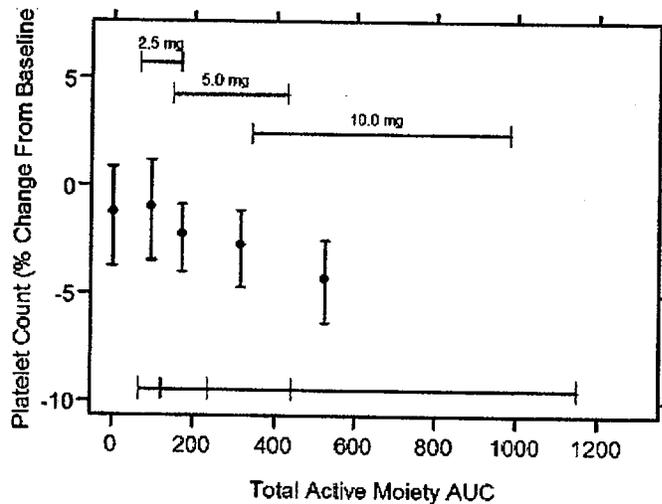


Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 12A

Data and error bars are plotted as mean \pm SEM.

Platelet count

Platelet count appears to gradually decrease with increasing saxagliptin exposure. The clinical relevance of these changes is discussed in Section 7. The Figure below depicts the Exposure-Response Relationship for Platelet Count; data for this figure were extracted from the pharmacometric analysis and Study CV181011.



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 12A

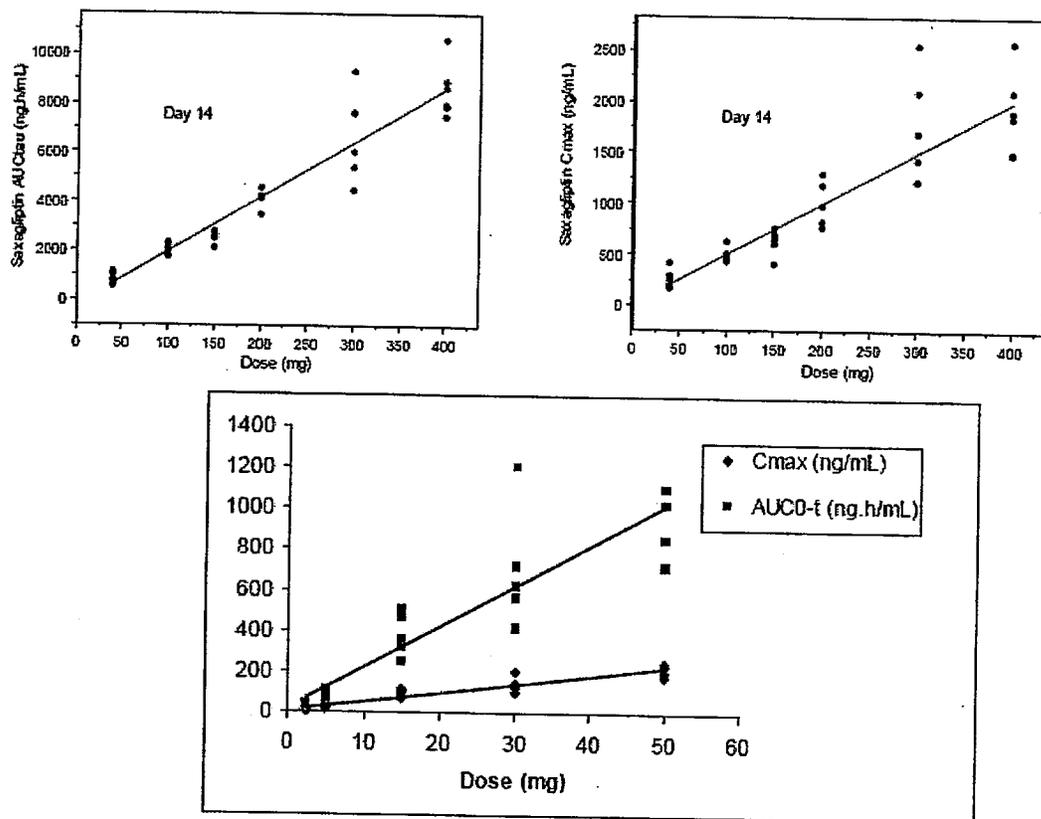
Mean percent change from baseline in lymphocyte count at week 24 for each quartile of exposure (AUC) are plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% CIs for the AUC for total active moiety for each dose are plotted as lines indicating the range of response for the expected distribution of AUC values within each dose. The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.

4.4.3 Pharmacokinetics

In humans, saxagliptin has a major active metabolite, BMS-510849, which is present in plasma at levels 2 to 7 times the level of the parent drug. This metabolite is also a DPP-4 inhibitor, but is two times less potent than saxagliptin. Saxagliptin and BMS-510849 exhibited selectivity for DPP-4 over DPP-8, and for DPP-4 over DPP-9.

The absolute bioavailability of saxagliptin was not determined. The AUC and C_{max} increased linearly following single and multiple dose administration with doses of 2.5 to 400 mg. This is shown in Figure 4.4 below. The time to reach C_{max} ranged from 1.5 to 4 hours following a 5 mg dose given once daily for 14 days in type 2 diabetics. Absorption was slightly delayed in the presence of food. In a mass balance study in healthy subjects, 74.9% of dose (% total radioactivity) was in the urine and approximately 22% in feces. The exposure of the main metabolite BMS-510849 was 3.1 times higher than the parent drug.

Figure 4.4. Saxagliptin AUC and Cmax on Day 14 in Healthy Volunteers (top) and Type 2 Diabetics (bottom)



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 18

The serum protein binding for saxagliptin and the metabolite BMS-510849 was negligible in all species tested.

Saxagliptin is extensively metabolized via both metabolic and renal pathways, while BMS-510849 is primarily excreted by a renal pathway. Saxagliptin is mainly hydrolyzed by CYP450 3A4/5 enzymes to form BMS-510849. The mean elimination half-life after multiple oral administrations in patients was between 2.3-3.3 hours following 2.5 mg and 5 mg doses. Saxagliptin is almost completely eliminated within 24 hours post-dose.

Saxagliptin is proposed to be administered without regard to food. In the definitive food effect study, in which the 10 mg tablet was used, there was an approximately 27% increase in saxagliptin AUC with a high-fat meal. However, this was not considered clinically significant. The T_{max} was also delayed in the presence of food (median T_{max} of 0.99 h with meal as compared to 0.53 h). Therefore, the Sponsor's dosing administration approach is considered acceptable. The Sponsor requested a biowaiver for conducting additional clinical food effect

studies with the proposed to-be-marketed 2.5 mg and 5 mg tablets and to apply the findings from the 10 mg food effect study to the lower strength tablets.

Reviewer comment: According to Dr. Vaidyanathan, given the similarity of composition of the 3 dosage tablets, the linearity in saxagliptin PK in this dose range, and the similar dissolution profiles of all 3 strengths, a biowaiver can be granted.

Exposure in Different Demographic Groups

Age and Gender

Elderly subjects had higher systemic exposures to saxagliptin and BMS-510849 (60% and 35% higher, respectively) compared to young subjects. Adjustment for creatinine clearance and body weight reduced the saxagliptin PK difference between elderly and young to 12%, 29%, and 30% for C_{max} , AUC_{inf} , and $AUC_{(0-T)}$, respectively.

Reviewer comment: According to Dr. Vaidyanathan, since the majority of saxagliptin that is not cleared renally is likely to be metabolized, the balance of the difference in saxagliptin systemic clearance is probably due to a decreased metabolic capacity with increased age.

There was interaction between age and sex on saxagliptin exposure as seen by an 84-87% increase in elderly females versus young males. There was also a 68-70% increase in BMS-510849 exposure in elderly female subjects. Elderly males had increases of approximately 20%, 72%, and 74% in saxagliptin C_{max} , AUC_{inf} , and $AUC_{(0-T)}$, respectively, versus young males. A 20% increase in AUCs of BMS-510849 was also seen in elderly males compared to their young counterparts.

Reviewer comment: As a comparison, the increase in presence of CYP inhibitors (3.8-fold in AUC) was much greater than that seen with elderly subjects. No dose adjustment is proposed based on age and gender, and Dr. Vaidyanathan considers this acceptable.

Race

While clearance of saxagliptin appears unchanged across different races, clearance of BMS-510849 appears to be increased (Asian or American Indian/Alaskan natives) or decreased (Hispanic/Latino) for specific race groups. Limitations to this analysis include the small numbers of subjects in each race group.

Reviewer comment: Given that the changes in clearance occur with the active metabolite, which is half as potent as saxagliptin, Dr. Vaidyanathan concludes that there is insufficient support for labeling adjustment.

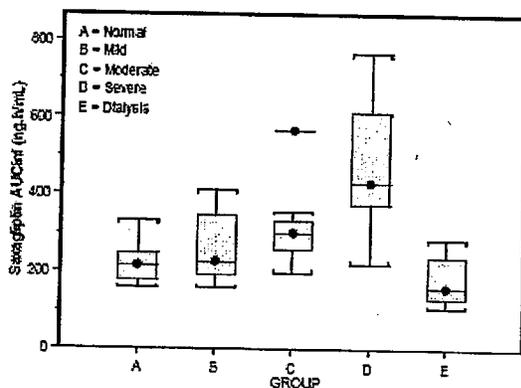
Exposure in Patients with Organ Failure

Renal Impairment

Renal function has a significant effect on saxagliptin exposure. In subjects with mild, moderate, and severe renal impairment, saxagliptin AUC increased by 15%, 40%, and 110% (2.1 fold), respectively, compared to control subjects. C_{max} in these subjects also increased by 39%, 7%, and 38% compared to normal subjects. Compared to subjects with normal renal function, subjects on hemodialysis (saxagliptin administered prior to the day's dialysis session) had 15%,

21% and 23% lower C_{max} , AUC_{inf} , and $AUC_{(0-t)}$ values. Figure 4.5 graphically compares saxagliptin AUC in normal and subjects with renal impairment.

Figure 4.5. Saxagliptin AUC in subjects with normal renal function and those with renal impairment



Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Figure 22

The exposure to metabolite BMS-510849 also increased significantly in subjects with renal impairment. Compared to subjects with normal renal function, subjects with mild, moderate, severe, and end-stage renal impairment had 40%, 47%, 46%, and 36% respectively, higher mean C_{max} values of the metabolite. Higher mean AUC values of BMS-510849 of 67%, 191% (2.9-fold), 347% (4.5-fold), and 306% (4.1-fold), respectively, were seen in mild, moderate, severe, and end-stage renal disease.

Table 4.2 summarizes changes in saxagliptin and BMS-510849 in renal impairment. The Sponsor has proposed 2.5 mg for moderate, severe and ESRD patients and no dosage adjustments are being proposed for mild renal impairment.

Reviewer comment: The Sponsor's proposal is acceptable, according to the Clinical Pharmacology Reviewer.

Table 4.2. Changes in saxagliptin and metabolite BMS-510849 in renal impairment

	Metabolite BMS-510849 AUC ratio compared to healthy	Parent AUC ratio compared to healthy	Molar ratio (AUC Metabolite/AUC Parent) x (455.55/487.55)
Healthy	–	–	2.44
Mild	1.71	1.18	3.51
Moderate	3.18	1.44	5.40
Severe	4.52	2.15	5.11
ESRD	4.18	0.81	12.56

Source: Dr. Vaidyanathan's Clinical Pharmacology Review, Table 13

Hepatic Impairment

Saxagliptin is metabolized in the liver by CYP3A and the exposure is expected to increase in hepatic impairment. For the mild hepatic impairment group, the geometric means for saxagliptin C_{max} , AUC_{inf} and $AUC_{(0-t)}$ were 8%, 10%, and 10% higher, respectively, compared to healthy subjects; for the moderate impairment group these parameters were 2%, 38%, and 38% higher; finally, for the severe impairment group, C_{max} was 6% lower, while AUC_{inf} and $AUC_{(0-t)}$ were 77% and 72% higher.

For the metabolite BMS-510849, generally all PK parameters for subjects with hepatic impairment (all groups) were decreased compared to healthy subjects.

Reviewer comment: According to Dr. Vaidyanathan, this observation for the metabolite indicates a reduced capacity to metabolize saxagliptin as hepatic function declines.

Overall, the Sponsor's conclusions regarding no dosage adjustments based on hepatic function are acceptable.

Drug-drug Interactions

Because saxagliptin is a CYP3A4/5 substrate as well as a P-glycoprotein substrate, the effect of strong CYP3A inhibitors and inducers on saxagliptin concentrations is an important issue. Drug-drug interaction (DDI) was evaluated with the following: ketoconazole, diltiazem, rifampin, Maalox® Max, famotidine, omeprazole, glyburide, pioglitazone, metformin, digoxin, and simvastatin. The most significant changes in saxagliptin exposure occurred in the presence of metabolic modulators. The DDI with ketoconazole, conducted with 100 mg and 20 mg saxagliptin, revealed a 2.5-fold and 3.8-fold increase in saxagliptin exposure, respectively. The true extent of exposure increase with saxagliptin 5 mg remains unknown. Particularly when considering the adverse events associated with ketoconazole (discussed in Section 7, lymphocytes), it is recommended that the dose of saxagliptin be reduced to 2.5 mg when patients are prescribed CYP3A4/5 inhibitors.

There was also a statistical decrease in C_{max} of saxagliptin in the presence of Maalox® Max (26% decrease) and metformin (21% decrease). The 90% CI for these drugs fell outside of the 80-125% limit for C_{max} in the presence of these drugs with no impact on the AUC of saxagliptin.

Reviewer comment: According to Dr. Vaidyanathan, the changes associated with Maalox® Max and metformin are unlikely to be clinically significant.

5 Sources of Clinical Data

This review uses clinical data derived from the Sponsor's studies. Table 5.1 summarizes saxagliptin clinical studies (excluding safety and efficacy studies), while Table 5.2 summarizes safety and efficacy studies.

There were 27 Clinical Pharmacology studies. These include:

- 1) Ascending dose studies
- 2) Biopharmaceutical studies
- 3) Thorough corrected QT interval (QT_c) study
- 4) Drug-drug interactions with other antihyperglycemic agents, drug metabolizing enzyme inhibitors and probe drugs
- 5) Pharmacokinetic studies in relation to age, gender, hepatic impairment, and renal impairment
- 6) Pharmacokinetic studies of saxagliptin delivered in various formulations
- 7) Population pharmacokinetic analysis

There were eight Phase 2b/3 studies:

- 1) Six randomized, double-blind, placebo- or active-controlled key efficacy studies
- 2) One Phase 2b dose-finding study
- 3) One Phase 3 mechanism of action (MOA) study

In addition, there are 3 ongoing Phase 3 studies:

- 1) Safety and efficacy of saxagliptin + metformin vs. sulfonylurea + metformin (CV181054)
- 2) Safety and efficacy of saxagliptin + metformin vs. sitagliptin + metformin (CV181056)
- 3) Saxagliptin vs. placebo in adult patients with type 2 DM and moderate, severe, and end-stage renal impairment (CV181062)

5.1 Tables of Clinical Studies

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	Single dose
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	14 days
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	Single dose
181004	¹⁴ C ADME	Open-label single dose	Healthy N=6	PK, mass balance, metabolism, safety	Saxa 50mg, ¹⁴ C metabolism	Single dose
181005	Drug interaction	Open-label single sequence	Healthy N=15	Drug-drug interaction with ketoconazole	Saxa 100mg qd with 200mg q12h ketoconazole	12 days
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	14 days
181017	Drug interaction	Open-label, randomized, 3-period, 3-	Healthy N=18	Drug-drug interaction with met, safety	Saxa 100mg and Met 1000mg	Single dose

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			treatment, cross-over study balanced for residual effects						
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	Single dose	
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	Single dose	
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	Single dose	
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	Single dose	
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	12 days	
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	5 days	
181027	Drug interaction		Open-label, randomized, 3-period, 3-treatment, cross-	Healthy N=14 (0 completed, terminated early)		Drug-drug interaction with digoxin, safety	Multiple regimens using saxa 5mg and digoxin	30 days, terminated early due to dosing error	

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181028	Drug interaction	over Open-label, non-sequential	Healthy N=30		Drug-drug interaction with pioglitazone	Saxa 10mg and pioglitazone 45mg	13 days
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	23 days
181032	Thorough QTc study	Randomized, double-blind, placebo-controlled, 4-period, 4-treatment, crossover	Healthy N=40		ECG effects of saxa; PK	Saxa 10 or 40mg qd, Moxifloxacin 400mg qd	16 days
181033	Drug interaction	Open-label, non-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-	Healthy N=16		Relative bioavailability,	Saxa 5mg tablet versus Saxa 5mg	Single dose

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			period, 2-treatment, crossover			capsule	
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	
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	Single dose and multiple dose	

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=saxagliptin; T=short-term; SU=sulfonylurea; T2DM=type 2 diabetes mellitus; wks=weeks

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Table 5.2. Saxagliptin Safety and Efficacy Studies						
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, Status if ongoing
181008	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled	Type 2 DM Drug naïve N=361	Safety and efficacy	Saxa 2.5, 5, 10, 20, and 40mg for 12 weeks or 100mg or PBO for 6 wks	12 or 6 week DB, 4 week follow-up
181011	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled	Type 2 DM Drug naïve N=290	Safety and efficacy	Saxa 2.5mg, 5mg, or 10mg	24 weeks with LT extension to ≥18 months, LT ongoing
181013	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled study with LT extension	Type 2 DM TZD failure N=437	Safety and efficacy	OL TZD + Saxa 2.5mg, 5mg, or OL TZD + PBO	24 weeks with LT extension ≥12 months, LT ongoing
181014	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled study with LT extension	Type 2 DM Met failure N=543	Safety and efficacy	OL Met + Saxa 2.5mg, 5mg, 10mg or OL Met + PBO	24 weeks with LT extension ≥12 months, LT ongoing
181038	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled	Type 2 DM Drug naïve N=272	Safety and efficacy	Saxa 2.5mg qam, 2.5mg titrated to 5mg qam, 5mg qam, 5mg qpm, or PBO	24 weeks with LT extension ≥12 months, LT ongoing
181039	Safety and efficacy	Randomized,	Type 2 DM	Safety and	Saxa 5mg or 10mg +	24 weeks with

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			parallel-group, double-blind, active-controlled	Drug naïve N=991	efficacy	Met 500mg; or Saxa 10mg; or Met 500mg	LT extension ≥12 months, LT ongoing
181040	Safety and efficacy	Randomized, parallel-group, double-blind, placebo-controlled	Type 2 DM SU failure	Safety and efficacy	OL Gly 7.5mg + Saxa 2.5mg, 5mg or PBO + Gly 10mg	24 weeks with LT extension ≥12 months, LT ongoing	
181041	Mechanism of action	Randomized, parallel-group, double-blind, placebo-controlled study with LT extension	Type 2 DM Drug naïve	Efficacy (effects on insulin secretion and related parameters) and safety	Saxa 5mg versus PBO	12 weeks with LT extension ≥104 weeks	
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	52 weeks with 52-week extension, ongoing	
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	18 weeks, ongoing	
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=saxagliptin; ST=short-term; SU=sulfonylurea; TZDM=type 2 diabetes mellitus; wks=weeks

5.2 Review Strategy

Source of clinical data in this review are the original NDA submission, the 120-day safety update, and a number of responses to FDA requests for information.

In the safety evaluation, all Phase 2b/3 safety and efficacy studies were used. Nevertheless, I placed emphasis on the Core Phase 3 studies, since the Phase 2b dose-finding study and the Phase 3 MOA study were smaller and shorter in duration, limiting their contribution to safety data. Although both short-term and long-term periods of the Core Phase 3 studies were reviewed, some safety analyses focus on the short-term period, while others, particularly those of rarer events, utilize both periods. Although the long-term period retained subjects on double-blind therapy in addition to open-label rescue therapy, the numbers of subjects decreased, in some studies, significantly beyond Week 24, thereby limiting the utility of these analyses. It should also be noted that the Sponsor presented safety results in 2 categories of subjects: 1) prior to rescue and 2) regardless of rescue. These are specified in the safety review and are important when analyzing for confounding factors.

In the efficacy evaluation, the Core phase 3 studies were primarily used with support from the Phase 2b dose-finding study (CV181008) and the Phase 3 MOA (181041) study. Details for Study CV181008 can be found Sections 4.4 and 10, while those for Study CV181041 can be found in Section 10.

5.3 Discussion of Individual Studies

The clinical program evaluating the efficacy of saxagliptin in subjects with type 2 diabetes included a Phase 2b dose-finding study (CV181008) and 7 Phase 3 controlled clinical studies. Six of these 7 were pivotal efficacy and safety studies (CV181011, CV181038, CV181014, CV181039, CV181013, and CV181040) and are considered the Core Phase 3 studies. The seventh study (CV181041) evaluated the mechanism of action of saxagliptin. Among these 8 studies, a total of 4673 subjects were randomized and treated: 3422 exposed to saxagliptin, 656 exposed to placebo, 328 exposed to metformin (CV181039), and 267 exposed to up-titrated glyburide (CV181040). Table 5.3 summarizes the Phase 2b and 3 Studies.

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Table 5.3. Overview of Phase 2b and 3 Studies

Study	Target Population/ A1c at Screening	ST Treatment Groups	LT Treatment Groups	Rescue Treatment	Duration (Weeks) ST/LT/Total
Pooled Monotherapy Analysis					
CV181011					
Phase 3	Treatment naïve subjects	<u>4</u> Groups: Saxa (2.5, 5, and 10mg) or Placebo OL: Saxa 10mg	<u>4</u> Groups: Saxa (2.5, 5, and 10mg) or Met 500mg OL: Saxa 10mg	Met 500mg (titratable to 2000mg)	24/182/206
N=401 (+66 received Saxa 10mg OL)	(7-10% DB); (10-12% OL)				
CV 181038	Treatment naïve subjects	<u>5</u> Groups: Saxa (2.5mg qam, 2.5/5mg qam, 5mg qam, and 5mg qpm) or Placebo	<u>5</u> Groups: Saxa (2.5mg qam, 2.5/5mg qam, 5mg qam, and 5mg qpm) or Met 500mg (Saxa could be titrated to 10mg per protocol)	Met 500mg (titratable to 2000mg)	24/52/76
Phase 3 N=365	(7-10%)				
Add-on Combination Therapy					
CV181014	Met failure subjects:	<u>4</u> Groups: OL Met + Saxa (2.5, 5, and 10mg) or Placebo	<u>4</u> Groups: OL Met + Saxa (2.5, 5, and 10mg) or Placebo	Pioglitazone 15mg (titratable to 30 or 45mg)	24/182/206
Phase 3 N=743	(Met 1500-2550mg TDD) (7-10%)				
CV181040	SU failure subjects:	<u>3</u> Groups: OL Gly 7.5mg + Saxa 2.5 or 5mg; or OL Gly 7.5mg + DB Gly 2.5mg (TDD of Gly 10mg, titratable to 15mg) + placebo	<u>3</u> Groups: OL Gly 7.5mg + Saxa 2.5 or 5mg; or OL Gly 7.5mg + DB Gly 2.5-7.5mg (titratable to a maximum of 20mg TDD) + Placebo	Met 500mg (titratable to 2500mg)	24/52/76
Phase 3 N=743	4 week lead in Gly 7.5mg (7.5-10%)				
CV181013	TZA failure subjects:	<u>3</u> Groups: OL TZD + Saxa 2.5 and 5mg or Placebo	<u>3</u> Groups: OL TZD + Saxa 2.5 and 5mg or Placebo	Met 500mg (titratable to 2500mg)	24/52/76
Phase 3 N=565	Rosi 4 or 8mg or Plo 30 or 45mg (7-				

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10.5%	
Combination Therapy (Initial or First Line Therapy)	
	4 Groups:
CV181039 Phase 3 N=1306	Treatment naïve subjects (8-12%) Placebo + Met IR; Placebo + Saxa 10mg; Saxa 5mg + Met IR, Saxa 10mg + Met IR (Met titratable 500-2000mg per protocol) Placebo + Met IR; Placebo + Saxa 10mg; Saxa 5mg + Met IR; Saxa 10mg + Met IR Pio 15mg (titratable to 45mg) 24/52/76
Other Studies	
CV181008 Phase 2b N=423	Main Cohort: 6 Groups: Saxa 2.5, 5, 10, 20, 40mg or placebo Protocol Amendment 4: 2 groups added: Saxa 100mg or Placebo NA 12/NA/16 (0-40mg Cohort) 6/NA/10 (0, 100mg Cohort)
CV181041 Phase 3 MOA N=36	2 Groups: Saxa 5mg or Met 500mg (titrated to 1000mg TDD per protocol) NA 12/104/116

qam-morning dosing; qpm=evening dosing; 2.5/5mg=titration from 2.5 to 5mg
 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: Sponsor's Summary of Clinical Safety, Table 1.1B

Phase 2b dose-finding Study

Study CV181008 was designed to evaluate the safety and efficacy of saxagliptin monotherapy in treatment-naïve subjects who had inadequate glycemic control. Subjects were randomized to receive 1 of 5 doses of saxagliptin (2.5, 5, 10, 20, and 40mg) or placebo once daily for 12 weeks. An additional cohort was randomized to receive saxagliptin 100mg or placebo once daily for 6 weeks. Details of the study design are included in the Appendix, and results are summarized in Section 4.4.

Phase 3 Efficacy Studies

Three doses of saxagliptin (2.5, 5, and 10mg) were evaluated for safety and efficacy in 6 double-blind, randomized controlled studies in the Phase 3 clinical program. Two studies, CV181011 and CV181038, evaluated the safety and efficacy of saxagliptin as monotherapy in treatment-naïve subjects with inadequate glycemic control. Studies CV181013, CV181014, and CV181040 evaluated the safety and efficacy of saxagliptin in combination with metformin, SU, or TZD alone. Study CV181039 evaluated the safety and efficacy of saxagliptin in combination with metformin as initial therapy versus initial therapy with saxagliptin or metformin as monotherapies. The seventh Phase 3 study, CV181041, evaluated the effect of saxagliptin on biomarkers of β -cell function in treatment-naïve subjects with T2DM. The overall study design for the Core Phase 3 Studies is shown below. The primary assessment point was at 24 weeks. At that point, subjects were eligible to remain on randomized treatment and continue into a LT extension of at least 12 months. As of the NDA submission, the ST periods were completed and the LT extensions were ongoing. Subjects were eligible to enter the LT period either by completing all visits without requiring rescue (criteria discussed below) or meeting glycemic rescue criteria at any time in the ST treatment period, which was reported as an early discontinuation from the ST period for lack of efficacy.

Study CV181011 also included an open-label treatment group for subjects with screening A1c $>10\%$ and $\leq 12\%$ who received saxagliptin 10mg directly after screening. These subjects could be rescued and enter a LT period.

Three additional studies of saxagliptin have been initiated, but results have not submitted by the Sponsor:

- CV181054: To evaluate the safety and efficacy of saxagliptin in combination with metformin compared with SU in combination with metformin.
- CV181056: To evaluate the safety and efficacy of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin.
- CV181062: To evaluate the effect of saxagliptin compared with placebo in adult patients with T2DM and renal impairment (moderate, severe, and end-stage).

The Sponsor presented individual study results based on the primary and secondary efficacy endpoints. In addition, 2 data pools were developed that include:

1. the 2 monotherapy studies, referred to as “Pooled Monotherapy” (CV181011 and CV181038)

2. the 5 placebo-controlled studies, referred to as “Pooled Monotherapy/Add-on” (CV181011, CV181038, CV181013, CV181040 and CV181014)

All analyses on the efficacy parameters used the last observation carried forward (LOCF) methodology. Results of mean changes or mean percent changes from baseline reported refer to adjusted mean changes from baseline using ANCOVA methodology. All studies were designed as superiority studies.

Any data collected after rescue and initiation of additional oral anti-diabetic therapy was not utilized in any efficacy analyses. In order to be included in an analysis at any specific time point, the subject must have had a post-baseline measurement for the time point. If the subject was rescued, that measurement must have been taken before rescue. Criteria for rescue in each Core Phase 3 Protocol for the ST and LT periods are presented below in Tables 5.4-5.5, respectively.

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Table 5.4. 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					
FPG>220 mg/dL (central lab)	Week 8					
FPG>200 mg/dL (central lab)	Weeks 12, 16, 20, 24					
Mean FPG> 240 mg/dL Or MFWBG>221 mg/dL*	Week 6	Week 6	Week 6	Weeks 4,6	Week 6	Week 6
Mean FPG>220 mg/dL Or MFWBG>203 mg/dL*	Week 8					
Mean FPG>200 mg/dL Or MFWBG>185 mg/dL*	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.						
Source: Summary of Clinical Efficacy, Table 1.5A						

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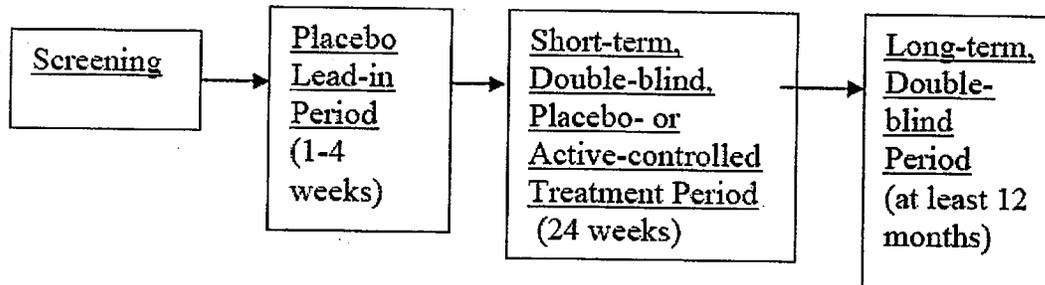
Table 5.5 Rescue Criteria for Lack of Glycemic Control for the LT Period of the Core Phase 3 Studies						
	CV181011	CV181038	CV181013	CV181040	CV181014	CV181039
A1c > 8.0%	Weeks 30, 37, 50	Weeks 30, 37, 50	Weeks 30, 37, 50	Weeks 30, 37, 50	Weeks 30, 37, 50	Weeks 30, 37, 50
A1c > 7.5%	Weeks 63, 76		Week 63	Week 63	Weeks 63, 76	Week 63
A1c > 7.0%	Weeks 89 to 193				Weeks 89 to 193	
A1c ≥ 7.0% and ≤ 8.0%		Weeks 30, 37, 50				
A1c ≥ 7.0% and ≤ 7.5%		Week 63				

Source: Summary of Clinical Efficacy, Table 1.5B

Study Design

The six Core phase 3 studies had the same overall design, depicted below.

Figure 5.1. Core phase 3 Study Design Overview



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

In these 6 studies, three doses of saxagliptin (2.5 mg, 5 mg and 10 mg) were evaluated. The Primary Efficacy Endpoint was the same: the change in A1c from baseline to Week 24 or the last post-baseline measurement prior to Week 24 and before rescue, if no Week 24 assessment was available. After the 24-week ST period, subjects were eligible to remain in randomized treatment and continue into a 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. Rescue criteria are outlined above.

5.3.1.1 Saxagliptin as Monotherapy

5.3.1.1.1 Study CV181011: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 Trial to evaluate the Efficacy and Safety of Saxagliptin as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Primary Objective: To compare, after short-term (24 weeks) oral administration of double-blind treatment, the change from baseline in hemoglobin A1c achieved with each dose of saxagliptin versus placebo in drug naïve subjects with type 2 diabetes who have inadequate glycemic control defined as A1c $\geq 7.0\%$ but $\leq 10.0\%$.

This was a multicenter (137 sites in the US, Puerto Rico, Canada, Mexico, Australia, and Taiwan), double-blind, placebo-controlled study. A total of 403 subjects with drug-naïve diabetes were randomized (1:1:1:1) and treated in the following groups, collectively termed Cohort 1:

- Saxagliptin 2.5mg (n=102)
- Saxagliptin 5mg (n=106)

Saxagliptin 10mg (n=98)
Placebo (n=95)

A second cohort of subjects, termed Cohort 2 (n=66), consisted of subjects with A1c >10.0% and ≤12.0% who were directly assigned to open-label treatment with saxagliptin 10mg.

Inclusion criteria included:

- 1) Men and non-nursing, non-pregnant women, 18 to 77 years of age.
- 2) Type 2 diabetes with inadequate glycemic control at screening ($\geq 7.0\%$ but $\leq 10.0\%$). Subjects with a screening A1c of $>10.0\%$ and $\leq 12.0\%$ were eligible for direct entry into an uncontrolled, OL phase.
- 3) Drug-naïve (never received medical treatment for diabetes or had received medical treatment for diabetes less than 6 months since original diagnosis).
- 4) Fasting C-peptide $\geq 1\text{ng/mL}$
- 5) BMI $\leq 40\text{ kg/m}^2$

Exclusion criteria included:

- 1) Women of childbearing potential (WOCBP) who were unwilling to use an acceptable method of contraception, or were pregnant or breastfeeding.
- 2) Symptoms of poorly controlled diabetes
- 3) History of diabetic ketoacidosis or hyperosmolar nonketotic coma
- 4) Insulin therapy within one year of screening
- 5) Significant cardiovascular history defined as:
 - a. History of myocardial infarction (MI), coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accidents within six months prior to study entry.
 - b. Congestive heart failure defined as NYHA stage III and IV and/or known left ventricular ejection fraction of $\leq 40\%$.
- 6) Chronic or repeated intermittent corticosteroid treatment
- 7) History of unstable or rapidly progressing renal disease
- 8) Active liver disease, infectious liver disease, and/or significant abnormal liver function defined as AST $> 2 \times \text{ULN}$ and/or ALT $> 2 \times \text{ULN}$ and/or serum total bilirubin $> 2.0\text{mg/dL}$.
- 9) Serum creatinine $\geq 1.5\text{mg/dL}$ for males and $\geq 1.4\text{mg/dL}$ for females
- 10) History of administration of any antihyperglycemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days during the 8 weeks prior to screening.
- 11) Use of any other antihyperglycemic medication after enrollment.

Following screening, subjects in Cohort 1 entered a 2 week lead-in period, followed by a 24-week double-blind short-term treatment period. Dose titration of blinded study drug was not permitted at any time during the study. Subjects with a lack of adequate glucose control during ST were eligible for the addition of open-label metformin as a rescue. The rescue criteria are shown below. Subjects who completed the ST period and subjects who met rescue criteria

entered the double-blind LT period (18 months). Subjects who were rescued from the ST period were reported as early discontinuations for lack of efficacy and entered the LT period.

Table 5.6 Rescue Criteria for Lack of Glycemic Control for the ST Period

Short Term Visit	Fasting Plasma Glucose (FPG)
Weeks 4 and 6	FPG > 240 mg/dL
Week 8	FPG > 220 mg/dL
Weeks 12, 16, 20, 24	FPG > 200 mg/dL

Source: Table 3.1.2, CSR CV181011

Those in Cohort 2 directly entered a 24-week open-label short-term treatment period and received saxagliptin 10mg. Dose titration was not permitted. As in Cohort 1, subjects were eligible for rescue with metformin.

Secondary efficacy endpoints:

- The change from baseline to Week 24 in FPG
- The proportion of subjects achieving A1c <7.0%
- The change from baseline in AUC from 0 to 180 minutes for postprandial glucose response to OGTT.

5.3.1.1.2 Study CV181038: A Multicenter, Randomized, Double-blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin as Monotherapy with Titration in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise

Primary Objective: To compare, after 24 weeks of oral administration of double-blind treatment, the change from baseline in HbA1c level achieved with saxagliptin 2.5mg qam, 5mg qam, and 2.5mg titrated to 5mg qam (2.5/5mg qam) versus placebo in drug-naïve subjects with type 2 diabetes who have inadequate glycemic control as defined as A1c ≥7.0% but ≤10.0% on diet and exercise.

This was a multicenter (72 sites in the US, Russia, India, and Taiwan), double-blind, placebo-controlled study. A total of 365 subjects with drug-naïve diabetes were randomized (1:1:1:1) and treated in the following groups:

- Saxagliptin 2.5mg qam (n= 74)
- Saxagliptin 2.5mg with possible titration to 5mg qam (2.5/5mg qam) (n=74)
- Saxagliptin 5mg qam (n=71)
- Saxagliptin 5mg qpm (n=72)
- Placebo (n=74)

This Protocol differed from the other monotherapy study described above in that it allowed for dose titration of saxagliptin.

The inclusion and exclusion criteria were identical to those in Study CV181011.

Following screening, subjects entered a 2-week, dietary and exercise placebo lead-in period, followed by randomization to a treatment group. Subjects who completed the ST period and subjects who met rescue criteria were eligible to enter the double-blind LT period for 12 months. During the ST period, subjects with inadequate glycemic control were eligible for the addition of metformin as rescue therapy. Rescue criteria were previously discussed in 6.1.1.1. Subjects who were rescued were reported as early discontinuations for lack of efficacy and entered the LT period. For subjects randomized to the 2.5/5mg qam treatment group, saxagliptin was titrated from 2.5mg to 5mg qam at Week 4, Week 8 or Week 12, based on pre-specified glycemic criteria. These subjects were also eligible for a second titration to 10mg qam at Week 24 prior to entering the LT period. Titration criteria were as follows:

Table 5.7 Titration Criteria

Visit	Mean Fasting Plasma Glucose	Mean Fasting Whole Blood Glucose
Week 4	≥150mg/dL	≥140mg/dL
Week 8	≥140mg/dL	≥131mg/dL and ≤203mg/dL
Weeks 12 and 24	≥126mg/dL and ≤200mg/dL	≥118mg/dL and ≤185mg/dL

Source: CSR CV181038

Subjects were eligible to enter the LT period via either of the following:

- a. Subjects completed all visits and did not meet rescue criteria in the ST period. Subjects who received saxagliptin in the ST were allowed to titrate saxagliptin in the LT to a maximum dose of 10mg (dose titration criteria discussed below). Subjects who received placebo in the ST received placebo and blinded metformin 500mg in the LT. Titration of blinded metformin was not allowed.
- b. Subjects who met rescue criteria during the ST period. These subjects remained on the same treatment assigned in the ST throughout the LT, but received open-label metformin in addition to blinded study drug. Titration of blinded study drug was not allowed, but titration of open-label metformin was permitted, to a maximum of 2000 mg/day.

For subjects who were not rescued, dose titration was performed in a blinded fashion at Weeks 30, 37, 50 and 63 according to pre-specified A1c parameters, shown below. This was performed regardless of previous titration in the ST.

Table 5.8. Saxagliptin Titration Criteria--Long-term Treatment Period

Visit	A1c
Weeks 30, 37, and 50	A1c ≥7.0% and ≤8.0%
Week 63	A1c ≥7.0% and ≤7.5%

Source: CV181038 Interim LT Study Report

In the LT period, subjects with lack of adequate glycemic control were eligible for rescue from continued hyperglycemia. All subjects requiring rescue during the LT period were assigned open-label metformin (500mg) which would be titrated, up to a maximum of 2000mg, as needed by the Investigator to achieve glycemic control. Those not controlled after 3 months on a maximally tolerated dose of metformin were discontinued from the study.

Secondary efficacy endpoints:

For the saxagliptin 2.5mg qam, 2.5/5mg qam, and 5mg treatment groups,

- a. Change from baseline in FPG
- b. Proportion of subjects achieving A1c<7.0%
- c. Change from baseline in AUC from 0 to 180 minutes for PPG response to an OGTT (week 24) in a subset of patients.

For the saxagliptin 5mg qam group,

- a. Change from baseline in A1c
- b. Change from baseline in FPG
- c. Proportion of subjects achieving A1c<7.0%
- d. Change from baseline in AUC from 0 to 180 minutes for PPG response to an OGTT (week 24) in a subset of patients.

5.3.1.2 Saxagliptin as Add-on Combination Therapy

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

Primary Objective: To compare, after 24 weeks of oral administration of double-blind treatment, the change from baseline in hemoglobin A1c achieved with each saxagliptin plus metformin treatment versus placebo plus metformin treatment in subjects with type 2 diabetes who have inadequate glycemic control defined as A1c $\geq 7.0\%$ and $\leq 10.0\%$ and currently treated with a stable metformin dose of at least 1500mg but not more than 2550 mg per day.

This was a multicenter, randomized, 4-arm, double-blind, placebo-controlled study in subjects with type 2 diabetes who had inadequate glycemic control (A1c $\geq 7.0\%$ and $\leq 10.0\%$) on a stable dose of metformin alone (1500mg to 2550mg). Following screening, subjects entered a 2-week lead-in period, during which subjects received metformin at their pre-study dose, up to 2500 mg daily. Subjects who had been receiving a dose exceeding 2500mg daily had their dose adjusted to 2500mg. Following the lead-in period, subjects were randomized (1:1:1:1) to 1 of 4 treatment arms and received the following in addition to their current dose of open-label metformin:

- saxagliptin 2.5mg (n=192)
- saxagliptin 5mg (n=191)
- saxagliptin 10mg (n=181)
- placebo (n=179)

Subjects who met glycemic rescue criteria during the ST period were eligible to enter the LT period where they received open-label pioglitazone added to their blinded study medication and

open-label metformin. Subjects who completed all visits during the ST period and did not meet glycemic rescue criteria were eligible to enter the LT period where they received the same treatment as they received during the ST period.

Inclusion and Criteria were identical to those listed for CV181011 except that subjects were required to be taking metformin 1500 mg-2550 mg during the 8 weeks prior to screening.

Rescue criteria are identical to those for CV181038.

Secondary Efficacy Endpoints: same as those listed for CV181011

5.3.1.2.2 *Study CV181040: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Glyburide in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Glyburide Alone*

Primary Objective: To compare after 24 weeks oral administration of double-blind treatment, the change from baseline in A1c achieved with each dose of saxagliptin plus glyburide versus placebo plus upward titrated glyburide.

This was a multicenter, randomized, 3-arm, double-blind, placebo-controlled study. After a 4-week lead-in period, subjects discontinued their current sulfonylurea therapy and began treatment with open-label glyburide 7.5 mg. Eligible subjects were then randomized (1:1:1) to 1 of 3 treatment arms for a 24-week, double-blind, placebo-controlled treatment period and received one of the following:

Saxagliptin 2.5 mg (n=248)

Saxagliptin 5 mg (n=253)

Placebo plus blinded glyburide 2.5mg in addition to open-label glyburide 7.5mg (n=267)

In subjects with hypoglycemia, the dose of open-label glyburide could be decreased once to 5mg per day during the ST period at the Investigator's discretion. In subjects assigned to the placebo/glyburide group, glyburide was titrated to 15mg total daily dose at Week 2 or Week 4 during the ST period, based on pre-specified glycemic criteria listed below and provided the dose of open-label glyburide had not been previously decreased due to hypoglycemia. Subjects who met glycemic rescue criteria during the ST period were eligible to enter the LT period (12 months) where they received open-label metformin in addition to their blinded study drug and open-label glyburide. Subjects who completed all ST visits and did not meet rescue criteria were eligible to enter the LT period where they received the same treatment as they received during the ST period.

Table 5.9. Titration Criteria for Subjects Assigned to Placebo Plus Upward Titrated Glyburide Treatment Group During The ST Double-blind Treatment Period

Upward Titration by Mean Fasting Glucose Criteria

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<u>Visit</u>	<u>MFPG mg/dL</u>	<u>MFWBG mg/dL</u>
Weeks 2 and 4	≥100 mg/dL	≥95 mg/dL

Inclusion Criteria were the same as those listed for CV181011 with the following exceptions:

- 1) Subjects with type 2 diabetes mellitus with inadequate glycemic control ($A1c \geq 7.5\%$ and $\leq 10.0\%$) requiring treatment with a submaximal dose of a sulfonylurea (defined as less than the maximum approved dose for each sulfonylurea, specific for each drug) for ≥ 2 months.
- 2) $A1c \geq 7.0\%$ and $MFPG \geq 140\text{mg/dL}$ or $MFWBG \geq 131\text{mg/dL}$ of FPG (central lab) $\geq 140\text{mg/dL}$ at randomization.

Exclusion Criteria were the same as those listed for CV181011 with the following exceptions:

- 1) History of administration of any antihyperglycemic therapy (other than a sulfonylurea) for more than 3 consecutive days or 7 non-consecutive days during the 12 weeks prior to screening.
- 2) Use of any other antihyperglycemic medication (other than 7.5mg glyburide or metformin) after entry into the lead-in period.

Secondary Efficacy Endpoints: same as those listed for CV181011

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

Primary Objective: To compare, after 24 weeks oral administration of double-blind treatment, the change from baseline in A1c achieved with each dose of saxagliptin plus TZA versus placebo plus TZD.

This was a randomized, 3-arm, parallel group, double-blind, placebo-controlled, multicenter study. Following a 2-week lead-in period, subjects were randomized (1:1:1) to 1 of 3 treatment arms in a 24-week double-blind, placebo-controlled period:

- Saxagliptin 2.5mg + current OL dose of TZD (n=195)
- Saxagliptin 5mg + current OL dose of TZD (n=186)
- Placebo + current OL dose of TZD (n=184)

Subjects who completed the ST period and subjects who met rescue criteria were eligible to enter the double-blind LT period.

Inclusion criteria: were the same as those listed for CV181011 with the following exceptions:

- 1) Receiving treatment with a stable monotherapy dose of a TZD (pioglitazone 30mg or 45mg daily; rosiglitazone 4mg daily or 8mg, either daily or in 2 divided doses of 4mg) for at least 12 weeks prior to screening.
- 2) After Amendment 3, A1c \geq 7.0% and \leq 10.5%
- 3) After Amendment 3, BMI \leq 45 kg/m²

Exclusion criteria were the same as those listed for CV181011 with the following exceptions:

- 1) History of administration of any antihyperglycemic therapy (other than pioglitazone 30mg or 45mg qd, or rosiglitazone 4mg qd, or 8mg, either QD or in 2 divided doses of 4mg) during the 12 weeks prior to screening.

Secondary Efficacy Endpoints: same as those listed for CV181011

5.3.1.3 Saxagliptin as Initial Combination Therapy

5.3.1.3.3 *Study CV181039: A Multicenter, Randomized, Double-blind, Active-controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin IR as Initial Therapy Compared to Saxagliptin Monotherapy and to Metformin IT Monotherapy in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control*

Primary Objective: To compare, after 24 weeks of oral administration of double-blind treatment, the change from baseline in Hemoglobin A1c achieved with each dose of saxagliptin + Metformin IR compared to saxagliptin + placebo and to metformin IR + placebo in subjects with type 2 diabetes who have inadequate glycemic control defined as A1c \geq 8% but \leq 12%.

This was a randomized, 4-arm, parallel group, double-blind, active-controlled, multi-center study in drug naïve subjects with inadequate glycemic control. Following screening, subjects entered a 1-week lead-in period. Subjects meeting criteria were then randomized (1:1:1:1) to one of the following:

- Saxagliptin 5mg + metformin IR 500mg (n=320)
- Saxagliptin 10mg + metformin IR 500mg (n=323)
- Saxagliptin 10mg + placebo (n=335)
- Metformin IR 500mg + placebo (n=328)

At Week 1, subjects receiving metformin as monotherapy or in combination with saxagliptin were to be titrated, as tolerated, from metformin 500mg/day to 1000mg/day in divided doses. At Weeks 2, 3, 4, and 5, subjects were to be titrated, as tolerated, in increments of 500mg up to a maximum of 2000mg/day in divided doses if mean FPG $>$ 110 mg/dL or MFWBG $>$ 104 mg/dL. Subjects who met glycemic rescue criteria during the ST period were eligible to enter the LT period (12 months) where they received open-label pioglitazone in addition to blinded study drug. Subjects who completed all visits during the ST period and did not meet glycemic rescue

criteria were eligible to enter the LT period where they received the same treatment as they did during the ST period.

Inclusion criteria were the same as those listed for CV181011 with the following exception:

- 1) Subjects with $A1c \geq 8\%$ but $\leq 12\%$ obtained at the screening visit.

Exclusion criteria were the same as those listed for CV181011.

Secondary objectives were the same as those listed for CV181011 plus the following 2 objectives:

- 1) Proportion of subjects achieving a therapeutic glycemic response defined as $A1c \leq 6.5\%$
- 2) Proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy within the 24 week, ST, double-blind treatment period.

6 Review of Efficacy

Efficacy Summary

See Ms. Joy Mele's Statistical Review for details.

Saxagliptin's clinical development program included 6 Core Phase 3 studies, which were all randomized, double-blinded, placebo- or active-controlled studies. These include 2 monotherapy studies, 3 add-on combination studies (to metformin, sulfonylurea, and thiazolidinedione), and one initial combination with metformin (ICM) study. The monotherapy studies and the ICM study were both conducted in treatment-naïve type 2 diabetics, while the add-on combination studies were conducted in subjects with uncontrolled diabetes on current medical therapy. One of the monotherapy studies (CV181038) compared saxagliptin dosing in the morning versus evening. All 6 Core phase 3 studies had a randomized, double-blind period of 24 weeks and a common primary efficacy endpoint: the change in HbA1c from baseline to Week 24. In these studies, the Sponsor used 3 doses of saxagliptin (2.5, 5, and 10 mg), allowing for further investigation of efficacy dose response.

Major secondary endpoints included: change from baseline in fasting plasma glucose (FPG), therapeutic glycemic response (defined as proportion of subjects achieving $A1c < 7.0\%$), and, in a subset of patients, the change from baseline in AUC from 0 to 180 minutes for PPG response to an OGTT. Two additional secondary endpoints were included in the ICM study (CV181039): the proportion of subjects achieving $A1c \leq 6.5\%$ at Week 24 and the proportion of subjects requiring rescue for failing to achieve pre-specified glycemic targets or discontinuing for lack of efficacy at Week 24.

Overall, modest efficacy was observed, and this is summarized in Table 6.1. For reference, the mean baseline HbA1c value for both monotherapy studies was 7.9%. The mean baseline A1c

values for the 3 add-on combination studies CV181013, CV181014, and CV181040 were 8.3, 8.0, and 8.4%, respectively. The mean baseline A1c value for Study CV181039 was 9.5%. In the pooled monotherapy studies, saxagliptin reduced HbA1c at Week 24 by 0.52-0.56% relative to placebo. No clear dose response was seen. Specifically, in Study CV181038, no efficacy difference was seen between the groups dosed in the morning versus the evening. Reductions in FPG relative to placebo were seen in saxagliptin-treated subjects in Study CV181011.

Among the add-on combination studies, greatest efficacy was seen in the add-on to metformin study (CV181014). In this study, saxagliptin reduced HbA1c by 0.72-0.83% relative to placebo. No dose response was seen. In the add-on combination study to glyburide, saxagliptin reduced HbA1c by 0.62-0.72%. In the add-on combination study to TZD, saxagliptin reduced HbA1c by 0.36-0.63% relative to placebo. In all 3 add-on combination studies, the greatest observed decreases in HbA1c occurred in the 5 mg combination groups.

In the ICM study, saxagliptin reduced HbA1c by 0.50-0.54% relative to metformin alone. No dose response was seen.

Across the Core Phase 3 studies, saxagliptin appeared to be weight-neutral.

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Table 6.1. HbA1c Changes from Baseline at Week 24 (LOCF) in Core Phase 3 Studies					
Study	Saxagliptin Treatment Groups	Control	Adjusted Mean Change from Baseline (%)	Difference in Adjusted Mean Change from Baseline vs. Control [95% CI]	
Monotherapy					
CV181011	Saxa 2.5 mg	Placebo	-0.43	-0.62 [-0.90, -0.33]	
	Saxa 5 mg	Placebo	-0.46	-0.64 [-0.93, -0.36]	
	Saxa 10 mg	Placebo	-0.54	-0.73 [-1.02, -0.44]	
	Saxa 10 mg OL	--	-1.87	--	
CV181038	Saxa 2.5 mg	Placebo	-0.71	-0.45 [-0.74, -0.16]	
	Saxa 5 mg	Placebo	-0.66	-0.40 [-0.69, -0.12]	
	Saxa 2.5/5 mg	Placebo	-0.63	-0.37 [-0.65, -0.08]	
	Saxa 5 mg QPM	Placebo	-0.61	-0.35 [-0.63, -0.07]	
Combination Therapy					
CV181013	Saxa 2.5 mg + TZD	Placebo + TZD	-0.66	-0.36 [-0.57, -0.15]	
	Saxa 5 mg + TZD	Placebo + TZD	-0.94	-0.63 [-0.84, -0.42]	
CV181040	Saxa 2.5 mg + Gly	Placebo + Uptitrated glyburide	-0.54	-0.62 [-0.78, -0.45]	
	Saxa 5 mg + Gly	Placebo + Uptitrated glyburide	-0.64	-0.72 [-0.88, -0.56]	
CV181014	Saxa 2.5 mg + Met	Placebo + metformin	-0.59	-0.73 [-0.92, -0.53]	
	Saxa 5 mg + Met	Placebo + metformin	-0.69	-0.83 [-1.02, -0.63]	
	Saxa 10 mg + Met	Placebo + metformin	-0.58	-0.72 [-0.91, -0.52]	

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Table 6.1. HbA1c Changes from Baseline at Week 24 (LOCF) in Core Phase 3 Studies

metformin		
Initial Combination Therapy		
Saxa 5 mg + Met	Metformin	-2.53
	Saxa 10 mg	-0.54 [-0.73, -0.35]
Saxa 10 mg + Met	Metformin	-2.53
	Saxa 10 mg	-0.84 [-1.03, -0.65]
Saxa 10 mg	None	-2.49
Metformin	None	-0.50 [-0.70, -0.31]
	None	-2.49
	None	-1.69
CV181039	Metformin	-1.99
	None	--
	None	--

Source: Summary of Clinical Efficacy, page 12

6.1 Indication

The Sponsor proposes saxagliptin as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus:

- As monotherapy
- In combination with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU) when the single agent alone, with diet and exercise, does not provide adequate glycemic control; and
- As initial combination therapy with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate.

6.1.1 Methods

The results of the Core Phase 3 studies were the primary data used in the efficacy analysis. These randomized, double-blind, placebo-controlled studies were of sufficient duration to allow for adequate assessment of the primary efficacy endpoint.

6.1.2 Demographics

Because ethnicity information was collected only for US subjects, the prevalence of Hispanic/Latino subjects enrolled was not adequately characterized. The limited data, therefore, are not presented here.

6.1.2.1 Monotherapy Population

The tables below summarize the baseline demographic and diabetes characteristics for subjects in the 2 pooled Monotherapy Studies (CV181011, CV181038). In general, treatment and placebo groups were well-matched with regard to age, gender, race, and BMI. Most subjects were less than 65 years old. There was a slight female predominance across all treatment groups. Most subjects were white, while Asians were the second most prevalent group. North America was the primary site of enrollment. The majority of subjects were obese (BMI > 30 kg/m²).

Table 6.2 Baseline demographic characteristics for subjects in Pooled Monotherapy studies					
	Saxa 2.5mg N=247	Saxa 5mg N=252	Saxa 10mg N=98	All Saxa N=597	Placebo N=169
Age					
Mean	54.2	54.5	52.7	54.1	54.6
Median	55	55	55	55	56
Min, Max	21.0, 77.0	18.0, 77.0	23.0, 75.0	18.0, 77.0	22.0, 77.0
Age group, N (%)					
<65	208 (84.2)	209 (82.9)	84 (85.7)	501 (83.9)	138 (81.7)
≥65	39 (15.8)	43 (17.1)	14 (14.3)	96 (16.1)	31 (18.3)
≥75	4 (1.6)	4 (1.6)	1 (1.0)	9 (1.5)	3 (1.8)
Gender, N (%)					
Male	120 (48.6)	125 (49.6)	45 (45.9)	290 (48.6)	82 (48.5)
Female	127 (51.4)	127 (50.4)	53 (54.1)	307 (51.4)	87 (51.5)
Race, N (%)					
White	193 (78.1)	190 (75.4)	80 (81.6)	463 (77.6)	132 (78.1)
Black	12 (4.9)	18 (7.1)	6 (6.1)	36 (6.0)	10 (5.9)
Asian	37 (15.0)	40 (15.9)	6 (6.1)	83 (13.9)	20 (11.8)
Other	5 (2.0)	4 (1.6)	6 (6.1)	15 (2.5)	7 (4.1)
Region					
N. America	146 (59.1)	148 (58.7)	75 (76.5)	369 (61.8)	107 (63.3)
L. America	17 (6.9)	17 (6.7)	17 (17.3)	51 (8.5)	15 (8.9)
Europe	48 (19.4)	49 (19.4)	0	97 (16.2)	27 (16.0)
Asia	36 (14.6)	38 (15.1)	6 (6.1)	80 (13.4)	20 (11.8)
Weight (kg)					
Mean	87.7	87.4	89.3	87.8	86.1
Median	86.6	86.2	89	87	83.9
Min, Max	44.5, 133.8	42.5, 141.8	47.9, 128.4	42.5, 141.8	50.7, 132.9
BMI (kg/m²)					
Mean	31.1	31.1	31.7	31.2	31
Median	31	31	32	31.1	30.7

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Table 6.2 Baseline demographic characteristics for subjects in Pooled Monotherapy studies

Min, Max	19.2, 44.2	19.9, 41.6	20.8, 40.5	19.2, 44.2	20.1, 39.9
BMI group (kg/m²), N (%)					
<30	105 (42.5)	108 (42.9)	35 (35.7)	248 (41.5)	73 (43.2)
≥30	142 (57.5)	144 (57.1)	63 (64.3)	349 (58.5)	96 (56.8)

Source: *Integrated Summary of Safety, Appendix 2.1.1*

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With regard to baseline diabetes characteristics, groups were also generally well-matched. The average baseline HbA1c for all saxagliptin groups was 7.9 versus 7.8 for the placebo groups. The mean duration of diabetes was 2.1-2.3 years across all groups. The placebo groups had a higher proportion of subjects with a baseline A1c < 8.0 (62.7% versus 56.1 for all saxagliptin groups).

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Table Baseline diabetes characteristics for Subjects in Monotherapy Studies					
	Saxa 2.5mg N=247	Saxa 5mg N=252	Saxa 10mg N=98	All Saxa N=597	Placebo N=169
Duration of diabetes (yrs)					
Mean (SD)	2.2 (2.97)	2.1 (3.74)	2.3 (3.10)	2.2 (3.33)	2.1 (2.75)
Median	0.9	0.7	1.1	0.8	0.7
Min, Max	0.0, 16.5	0.0, 40.6	0.0, 16.3	0.0, 40.6	0.0, 17.2
Duration of diabetes (yrs) n (%)					
≤1.5	148 (59.9)	157 (62.3)	61 (62.2)	366 (61.3)	99 (58.6)
≤3	176 (71.3)	193 (76.6)	67 (68.4)	436 (73.0)	122 (72.2)
>3-≤5	30 (12.1)	26 (10.3)	16 (16.3)	72 (12.1)	26 (15.4)
≥5	41 (16.6)	33 (13.1)	15 (15.3)	89 (14.9)	21 (12.4)
≥10	8 (3.2)	8 (3.2)	3 (3.1)	19 (3.2)	5 (3.0)
Baseline A1c (%)					
Mean (SD)	8.0 (0.95)	7.9 (0.98)	7.8 (0.90)	7.9 (0.95)	7.8 (0.95)
Median	7.8	7.8	7.7	7.8	7.6
Min, Max	5.3, 11.2	6.1, 10.6	6.1, 10.3	5.3, 11.2	5.8, 10.3
A1c Category (%) n (%)					
<8.0	138 (55.9)	140 (55.6)	57 (58.2)	335 (56.1)	106 (62.7)
≥8.0-<9.0	66 (26.7)	74 (29.4)	29 (29.6)	169 (28.3)	38 (22.5)
≥9.0	43 (17.4)	38 (15.1)	12 (12.2)	93 (15.6)	25 (14.8)
Fasting Plasma Glucose (mg/dL)					
Mean (SD)	169.9 (43.25)	165.8 (41.56)	177.5 (44.56)	169.4 (42.88)	166.6 (45.94)
Median	159	159	162	160	155
Min, Max	85.0, 319.0	91.0, 310.0	106.0, 315.0	85.0, 319.0	87.0, 318.0

Source: Integrated Summary of Safety, Appendix 2.1.1

In addition, pertinent baseline cardiovascular risk factors are presented by individual monotherapy study in Table 6.3. These data are presented unpooled as they were important in interpreting MACE results discussed in Section 7. In both studies, relatively few subjects had a history of coronary artery disease (CAD).

Table 6.3 Baseline Cardiovascular Risk Factors for Subjects in the Monotherapy Studies		
	CV181011	CV181038
	N=401	N=365
History of CAD	5%	13%
History of hypertension	48%	58%
Previous DM treatment	2.5%	5%
Used baseline CV medication?	45%	NA
HDL cholesterol (mg/dL)		
Mean (SD)	46 (10)	45 (9)
LDL cholesterol (mg/dL)		
Mean (SD)	115 (40)	122 (35)

Source: Individual Clinical Study Reports

6.1.2.2 Add-on Combination Studies

The tables below summarize the baseline demographic and diabetes characteristics for the 3 Add-on Combination Studies (CV181014, CV181040, CV181013), organized by individual study.

For CV181014 (metformin failure subjects), subjects were generally well-matched. With the exception of the saxagliptin 2.5mg + met group, there was a slight male predominance in the other groups. The majority of subjects were white, and enrollment was primarily in North America and Latin America. In all groups, the majority of subjects were obese.

For the 3 groups in CV181040, mean age was similar, but the Placebo + glyburide group had a slight predominance of subjects ≥ 65 years old. There was a female predominance in all groups, and most subjects were white. Latin America was the leading site of enrollment. In this study, the majority of subjects were not considered obese (majority had BMI < 30).

Finally, for CV181013, mean age for the 3 groups was similar. The saxagliptin 2.5 mg + TZD group was the only group with predominance of male subjects. For all groups, the majority of subjects were white or Asian. No European subjects were enrolled. The majority of subjects were not obese.

Table 6.4. Baseline Demographic Characteristics for Subjects in the 3 Add-on Combination Therapy Studies (CV181014, CV181040, CV181013)					
CV181014					
	Saxa 2.5mg + Met N=192	Saxa 5mg + Met N=191	Saxa 10mg + Met N=181	Placebo + Met N=179	Total N=743
Age					
Mean	54.66	54.68	54.18	54.75	54.57
Median	55	55	55	57	56
Min, Max	20.0, 76.0	31.0, 76.0	24.0, 77.0	26.0, 76.0	20.0, 77.0
Age group, N (%)					
<65	159 (82.8)	159 (83.2)	155 (85.6)	153 (85.5)	626 (84.3)
≥65	33 (17.2)	32 (16.8)	26 (14.4)	26 (14.5)	117 (15.7)
≥75	3 (1.6)	2 (1.0)	5 (2.8)	3 (1.7)	13 (1.7)
Gender, N (%)					
Male	83 (43.2)	103 (53.9)	95 (52.5)	96 (53.6)	377 (50.7)
Female	109 (56.8)	88 (46.1)	86 (47.5)	83 (46.4)	366 (49.3)
Race, N (%)					
White	153 (79.7)	159 (83.2)	144 (79.6)	150 (83.8)	606 (81.6)
Black	8 (4.2)	11 (5.8)	14 (7.7)	7 (3.9)	40 (5.4)
Asian	8 (4.2)	3 (1.6)	5 (2.8)	4 (2.2)	20 (2.7)
Other	23 (12.0)	18 (9.4)	18 (9.9)	18 (10.1)	77 (10.4)
Region					
N. America	108 (56.3)	108 (56.5)	102 (56.4)	94 (52.5)	412 (55.5)
L. America	79 (41.1)	80 (41.9)	77 (42.5)	81 (45.3)	317 (42.7)
Europe	0	0	0	0	0
Asia	5 (2.6)	3 (1.6)	2 (1.1)	4 (2.2)	14 (1.9)
Weight (kg)					
Mean	85.97	87.27	87.83	87.14	87.04
Median	84.5	85.5	86.9	88.1	86
Min, Max	52.70, 134.30	42.20, 145.10	44.50, 145.60	46.00, 141.00	42.20, 145.60
BMI (kg/m²)					
Mean	31.68	31.23	31.12	31.57	31.4
Median	31.39	30.6	30.55	31.24	30.96
Min, Max	21.30, 42.51	19.80, 41.22	18.93, 41.20	21.74, 41.68	18.93, 42.51
BMI group (kg/m²), N (%)					
<30	75 (39.1)	84 (44.0)	82 (45.3)	76 (42.5)	317 (42.7)
≥30	117 (60.9)	107 (56.0)	99 (54.7)	103 (57.5)	426 (57.3)

Table 6.4. Baseline Demographic Characteristics for Subjects in the 3 Add-on Combination Therapy Studies (CV181014, CV181040, CV181013)				
CV181040				
	Saxa 2.5mg + Gly N=248	Saxa 5mg + Gly N=253	Pla + Gly N=267	Total N=768
Age				
Mean	55.36	54.85	55.06	55.09
Median	56	56	56	56
Min, Max	30.0, 77.0	25.0, 77.0	18.0, 76.0	18.0, 77.0
Age group, N (%)				
<65	205 (82.7)	211 (83.4)	215 (80.5)	631 (82.2)
≥65	43 (17.3)	42 (16.6)	52 (19.5)	137 (17.8)
≥75	4 (1.6)	3 (1.2)	5 (1.9)	12 (1.6)
Gender, N (%)				
Male	113 (45.6)	110 (43.5)	123 (46.1)	346 (45.1)
Female	135 (54.4)	143 (56.5)	144 (53.9)	422 (54.9)
Race, N (%)				
White	148 (59.7)	151 (59.7)	152 (56.9)	451 (58.7)
Black	5 (2.0)	7 (2.8)	7 (2.6)	19 (2.5)
Asian	42 (16.9)	46 (18.2)	51 (19.1)	139 (18.1)
Other	53 (21.4)	49 (19.4)	57 (21.3)	159 (20.7)
Region				
N. America	36 (14.5)	39 (15.4)	43 (16.1)	118 (15.4)
L. America	162 (65.3)	162 (64.0)	165 (61.8)	489 (63.7)
Europe	10 (4.0)	11 (4.3)	12 (4.5)	33 (4.3)
Asia	40 (16.1)	41 (16.2)	47 (17.6)	128 (16.7)
Weight (kg)				
Mean	75.19	76.22	75.56	75.66
Median	74.3	73.3	73.5	73.85
Min, Max	45.0, 126.6	40.3, 133.4	43.4, 149.7	40.3, 149.7
BMI (kg/m²)				
Mean	29.10	29.19	28.83	29.04
Median	28.59	28.55	28.69	28.60
Min, Max	19.98, 40.77	17.44, 40.33	18.04, 40.99	17.44, 40.99
BMI group (kg/m²), N (%)				
<30	146 (58.9)	153 (60.5)	165 (61.8)	464 (60.4)
≥30	102 (41.1)	100 (39.5)	102 (38.2)	304 (39.6)
CV181013				

Table 6.4. Baseline Demographic Characteristics for Subjects in the 3 Add-on Combination Therapy Studies (CV181014, CV181040, CV181013)				
	Saxa 2.5mg + TZD N=195	Saxa 5mg + TZD N=186	Pla + TZD N=184	Total N=565
Age				
Mean	54.85	53.22	54.01	54.04
Median	55	54	54.00	55.00
Min, Max	25.00, 76.00	21.00, 76.00	30.00, 75.00	21.00, 76.00
Age group, N (%)				
<65	161 (82.6)	161 (86.6)	156 (84.8)	478 (84.6)
≥65	34 (17.4)	25 (13.4)	28 (15.2)	87 (15.4)
≥75	3 (1.5)	1 (0.5)	2 (1.1)	6 (1.1)
Gender, N (%)				
Male	106 (54.4)	89 (47.8)	85 (46.2)	280 (49.6)
Female	89 (45.6)	97 (52.2)	99 (53.8)	285 (50.4)
Race, N (%)				
White	109 (55.9)	99 (53.2)	101 (54.9)	309 (54.7)
Black	5 (2.6)	10 (5.4)	7 (3.8)	22 (3.9)
Asian	67 (34.4)	66 (35.5)	63 (34.2)	196 (34.7)
Other	14 (7.2)	11 (5.9)	13 (7.1)	38 (6.7)
Region				
N. America	91 (46.7)	81 (43.5)	83 (45.1)	255 (45.1)
L. America	44 (22.6)	41 (22.0)	40 (21.7)	125 (22.1)
Europe	0	0	0	0
Asia	60 (30.8)	64 (34.4)	61 (3.2)	185 (32.7)
Weight (kg)				
Mean	82.14	80.37	80.92	81.16
Median	76.00	79.80	77.55	78.00
Min, Max	44.80, 142.00	43.20, 146.50	43.00, 151.00	43.00, 151.00
BMI (kg/m²)				
Mean	30.03	29.77	30.32	30.04
Median	28.74	28.56	29.90	29.02
Min, Max	19.11, 45.25	19.19, 44.99	19.40, 44.52	19.11, 45.25
BMI group (kg/m²), N (%)				
<30	106 (54.4)	110 (59.1)	94 (51.1)	310 (54.9)
≥30	89 (45.6)	76 (40.9)	90 (48.9)	255 (45.1)

Source: Integrated Summary of Safety, Table 5.3.1

For the 3 add-on combination studies, subjects were also well-matched in their baseline diabetes characteristics. As expected, the duration of diabetes for subjects in all 3 add-on combination studies was longer than in the monotherapy studies or the initial metformin study.

For CV181014, the saxagliptin 10mg + metformin group had a greater proportion of subjects with an A1c < 8% compared to the other treatment groups.

For CV181040, mean A1c across the 3 groups was 8.4-8.5. The placebo + glyburide group had a disproportionately higher number of subjects with an A1c < 8.0% (59.1% versus 35.5% and 47.6% seen in the saxagliptin treatment groups) although the mean and median baseline A1c measurements in this group were similar to the corresponding values in the other treatment groups.

For CV181013, the mean A1c across the 3 groups was 8.2-8.4. The placebo + TZD group had a higher percentage of subjects with an A1c < 8.0%.

Table 6.5. Baseline diabetes characteristics for subjects in the 3 Add-on Combination Studies (CV181014, CV181040, CV181013)					
CV181014					
	Saxa 2.5mg + Met N=192	Saxa 5mg + Met N=191	Saxa 10mg + Met N=181	Placebo + Met N=179	Total N=743
Duration of diabetes (yrs)					
Mean					
(SD)	6.7 (5.6)	6.4 (4.7)	6.3 (4.4)	6.7 (5.6)	6.5 (5.1)
Median	5.4	5.5	5.5	5.2	5.4
Min, Max	0.1, 33.5	0.1, 25.4	0.2, 28.2	0.2, 35.9	0.1, 35.9
Duration of diabetes (yrs) n (%)					
≤1.5	25 (13.0)	14 (7.3)	18 (9.9)	22 (12.3)	79 (10.6)
≤3	48 (25)	47 (24.6)	34 (18.8)	53 (29.6)	182 (24.5)
>3-<5	37 (19.3)	41 (21.5)	44 (24.3)	36 (20.1)	158 (21.3)
≥5	107 (55.7)	103 (53.9)	103 (56.9)	90 (50.3)	403 (54.2)
≥10	42 (21.9)	36 (18.8)	31 (17.1)	47 (26.3)	156 (21)
Baseline A1c (%)					
Mean (SD)	8.1 (1.0)	8.1 (0.8)	8.0 (1.0)	8.1 (0.9)	8.0 (0.9)
Median	8	8	7.7	8	7.9
Min, Max	6.1, 12.0	6.5, 10.1	6.2, 11.3	6.1, 10.9	6.1, 12.0
A1c Category (%) n (%)					
<8.0	94 (49)	91 (47.6)	107 (59.1)	86 (48)	378 (50.9)
≥8.0-<9.0	63 (32.8)	69 (36.1)	43 (23.8)	62 (34.6)	237 (31.9)
≥9.0	35 (18.2)	31 (16.2)	31 (17.1)	31 (17.3)	128 (17.2)

Table 6.5. Baseline diabetes characteristics for subjects in the 3 Add-on Combination Studies (CV181014, CV181040, CV181013)					
Fasting Plasma Glucose (mg/dL)					
Mean (SD)	173.6 (44.3)	179.5 (47.3)	175.9 (50.2)	174.3 (43.5)	175.8 (46.4)
Median	166.5	173	162	169	168
Min, Max	90.0, 317.0	92.0, 347.0	67.0, 328.0	97.0, 306.0	67.0, 347.0
CV181040					
	Saxa 2.5mg + Gly N=248	Saxa 5mg + Gly N=253	Pla + Gly N=267		Total N=768
Duration of diabetes (yrs)					
Mean (SD)	7.1 (5.9)	6.8 (5.8)	6.8 (5.7)		6.9 (5.8)
Median	5.6	5.3	5.2		5.3
Min, Max	0.2, 29.5	0.0, 34.6	0.2, 31.4		0.0, 34.6
Duration of diabetes (yrs) n (%)					
≤1.5	42 (16.9)	46 (18.2)	38 (14.2)		126 (16.4)
≤3	70 (28.2)	72 (28.5)	78 (29.2)		220 (28.6)
>3-<5	36 (14.5)	41 (16.2)	46 (17.2)		123 (16)
≥5	142 (57.3)	140 (55.3)	143 (53.6)		425 (55.3)
≥10	69 (27.8)	61 (24.1)	61 (22.8)		191 (24.9)
Baseline A1c (%)					
Mean (SD)	8.4 (0.9)	8.5 (0.9)	8.4 (0.9)		8.4 (0.9)
Median	8.2	8.4	8.4		8.3
Min, Max	6.5, 11.5	6.8, 11.2	6.6, 11.4		6.5, 11.5
A1c Category (%) n (%)					
<8.0	88 (35.5)	91 (47.6)	107 (59.1)		86 (48)
≥8.0-<9.0	101 (40.7)	69 (36.1)	43 (23.8)		62 (34.6)
≥9.0	59 (23.8)	31 (16.2)	31 (17.1)		31 (17.3)
Not Reported	0 (0)	1 (0.4)	0 (0)		1 (0.1)
Fasting Plasma Glucose (mg/dL)					
Mean (SD)	170.2 (41.88)	175.1 (44.26)	174.6 (42.79)		173.3 (42.99)
Median	165.5	166.0	172.0		168.0
Min, Max	87.0, 328.0	75.0, 381.0	53.0, 306.0		53.0, 381.0

Table 6.5. Baseline diabetes characteristics for subjects in the 3 Add-on Combination Studies (CV181014, CV181040, CV181013)				
CV181013				
	Saxa 2.5mg + TZD N=195	Saxa 5mg + TZD N=186	Pla + TZD N=184	Total N=565
Duration of diabetes (yrs)				
Mean (SD)	5.3 (4.6)	5.2 (5.6)	5.1 (5.4)	5.2 (5.2)
Median	4.6	3.5	4.1	4.2
Min, Max	0.1, 24.2	0.2, 36.2	0.0, 41.2	0.0, 41.2
Duration of diabetes (yrs) n (%)				
≤1.5	47 (24.1)	55 (29.6)	56 (30.4)	158 (28)
≤3	72 (36.9)	87 (46.8)	83 (45.1)	242 (42.8)
>3-<5	34 (17.4)	24 (12.9)	22 (12)	80 (14.2)
≥5	89 (45.6)	75 (40.3)	79 (42.9)	243 (43)
≥10	28 (14.4)	26 (14)	22 (12)	76 (13.5)
Baseline A1c (%)				
Mean (SD)	8.3 (1.1)	8.4 (1.1)	8.2 (1.1)	8.3 (1.1)
Median	8.1	8.2	8	8.1
Min, Max	6.2, 12.4	6.0, 11.4	6.2, 13.0	6.0, 13.0
A1c Category (%) n (%)				
<8.0	88 (45.1)	77 (41.4)	90 (48.9)	255 (45.1)
≥8.0-<9.0	58 (29.7)	60 (32.3)	52 (28.3)	170 (30.1)
≥9.0	48 (24.6)	48 (25.8)	42 (22.8)	138 (24.4)
Not Reported	1 (0.5)	1 (0.5)	0 (0)	2 (0.4)
Fasting Plasma Glucose (mg/dL)				
Mean (SD)	163.2 (49.31)	159.9 (45.65)	174.6 (42.79)	173.3 (42.99)
Median	149.0	148.0	153.0	149.0
Min, Max	92.0, 331.0	48.0, 322.0	93.0, 345.0	48.0, 345.0

Source: Integrated Summary of Safety, Table 5.3.1

Pertinent baseline cardiovascular risk factors are presented below. As in the monotherapy studies, relatively few subjects had a history of CAD. All subjects in these add-on studies were on DM treatment at the time of randomization.

Table 6.6. Baseline Cardiovascular Risk Factors for Subjects in the Add-on Combination Studies			
	CV181014 N=743	CV181040 N=768	CV181013 N=565
History of CAD	3%	3%	4%

History of hypertension	59%	53%	55%
Previous DM treatment	100%	100%	100%
Used baseline CV medication?	58%	58%	53%
HDL cholesterol (mg/dL)			
Mean (SD)	47 (10)	44 (11)	46 (10)
LDL cholesterol (mg/dL)			
Mean (SD)	100 (32)	113 (34)	114 (36)

Source: Individual Clinical Study Reports

6.1.2.3 Initial Metformin Study

The tables below summarize the baseline demographic and diabetes characteristics for Study CV181039. In this study, treatment and comparator groups were well-matched for baseline demographic characteristics. The mean age across all groups was 51.8-52 years. The saxagliptin 10mg + Met treatment group had a slight female predominance (54.8%) compared to the other saxagliptin groups (48.4-49.6%) and metformin alone (50.3%). Most subjects were white. Europe and Latin America were the predominant sites of enrollment. The metformin alone group had a slight predominance of obese subjects (52.1% versus 50.4% for all saxagliptin groups).

	Saxa 5mg + Met N=320	Saxa 10mg + Met N=323	Saxa 10mg N=335	All Saxa N=978	Met N=328
Age					
Mean	52	52.1	52.1	52	51.8
Median	53	53	52	52.5	52.5
Min, Max	21.0, 76.0	23.0, 76.0	23.0, 76.0	21.0, 76.0	19.0, 77.0
Age group, N (%)					
<65	287 (89.7)	269 (83.3)	292 (87.2)	848 (86.7)	292 (89.0)
≥65	33 (10.3)	54 (16.7)	43 (12.8)	130 (13.3)	36 (11.0)
≥75	2 (0.6)	6 (1.9)	3 (0.9)	11 (1.1)	5 (1.5)
Gender, N (%)					
Male	165 (51.6)	146 (45.2)	169 (50.4)	480 (49.1)	163 (49.7)
Female	155 (48.4)	177 (54.8)	166 (49.6)	498 (50.9)	165 (50.3)
Race, N (%)					
White	246 (76.9)	243 (75.2)	255 (76.1)	744 (76.1)	251 (76.5)
Black	7 (2.2)	7 (2.2)	6 (1.8)	20 (2.0)	4 (1.2)

Asian	51 (15.9)	54 (16.7)	56 (16.7)	161 (16.5)	52 (15.9)
Other	16 (5.0)	19 (5.9)	18 (5.4)	53 (5.4)	21 (6.4)
Region					
N. America	57 (17.8)	55 (17.0)	54 (16.1)	166 (17.0)	50 (15.2)
L. America	87 (27.2)	90 (27.9)	97 (29.0)	274 (28.0)	96 (29.3)
Europe	126 (39.4)	126 (39.0)	132 (39.4)	384 (39.3)	130 (39.6)
Asia	50 (15.6)	52 (16.1)	52 (15.5)	154 (15.7)	52 (15.9)
Weight (kg)					
Mean	82.1	82.5	83.1	82.6	82.8
Median	82	82.1	82.4	82.1	83
Min, Max	43.0, 126.9	42.2, 155.1	43.1, 133.0	42.2, 155.1	36.8, 137.1
BMI (kg/m²)					
Mean	29.9	30.3	30.2	30.2	30.2
Median	29.7	30.2	30.2	30.1	30.2
Min, Max	18.6, 41.5	19.0, 40.9	18.2, 40.9	18.2, 41.5	15.4, 40.3
BMI group (kg/m²), N (%)					
<30	168 (52.5)	156 (48.3)	161 (48.1)	485 (49.6)	157 (47.9)
≥30	152 (47.5)	167 (51.7)	174 (51.9)	493 (50.4)	171 (52.1)

Source: Integrated Summary of Safety, Appendix 2.4.1

Subjects were also generally well-matched for baseline diabetes characteristics. Baseline A1c for all groups was generally higher than seen in other studies, as CV181039 randomized subjects with a higher upper limit of A1c (8-12%). In this study, the all saxagliptin group had a higher proportion of subjects with an A1c>9% (64.3% versus 58% for metformin alone).

	Saxa 5mg + Met N=320	Saxa 10mg + Met N=323	Saxa 10mg N=335	All Saxa N=978	Met N=328
Duration of diabetes (yrs)					
Mean (SD)	2.0 (3.65)	1.4 (2.54)	1.7 (2.83)	1.7 (3.05)	1.7 (3.13)
Median	0.4	0.3	0.4	0.4	0.4
Min, Max	0.0, 29.4	0.0, 15.4	0.0, 22.8	0.0, 29.4	0.0, 26.7
Duration of diabetes (yrs) n (%)					
≤1.5	214 (66.9)	247 (76.5)	227 (67.8)	688 (70.3)	224 (68.3)
≤3	257 (80.3)	277 (85.8)	267 (79.7)	801 (82.9)	267 (81.4)
>3-<5	22 (6.9)	18 (5.6)	30 (9.0)	70 (7.2)	25 (7.6)
≥5	41 (12.8)	28 (8.7)	38 (11.3)	107 (10.9)	36 (11.0)
≥10	12 (3.8)	7 (2.2)	8 (2.4)	27 (2.8)	11 (3.4)

Table 6.8. Baseline diabetes characteristics for Subjects in Initial Metformin Study (CV181039)					
Baseline A1c (%)					
Mean (SD)	9.4 (1.24)	9.5 (1.22)	9.6 (1.33)	9.5 (1.27)	9.4 (1.28)
Median	9.3	9.6	9.6	9.5	9.4
Min, Max	5.7, 12.8	6.3, 13.1	5.7, 12.8	5.7, 13.1	6.2, 13.4
A1c Category (%) n (%)					
<8.0	31 (9.7)	33 (10.2)	27 (8.1)	91 (9.3)	37 (11.3)
≥8.0-<9.0	92 (28.8)	74 (22.9)	87 (26.0)	253 (25.9)	98 (29.9)
≥9.0	195 (60.9)	216 (66.9)	218 (65.1)	629 (64.3)	193 (58.5)
Not Reported	2 (0.6)	0	3 (0.9)	5 (0.5)	1 (0.3)
Fasting Plasma Glucose (mg/dL)					
Mean (SD)	198.8 (56.57)	204.4 (59.74)	201.1 (54.80)	201.4 (57.03)	198.2
Median	190	195	194	194	186
Min, Max	93.0, 397.0	91.0, 449.0	92.0, 394.0	91.0, 449.0	70.0, 439.0

Source: Integrated Summary of Safety, Appendix 2.4.1

Table 6.9 summarizes additional cardiovascular risk factors for subjects in Study CV181039. As seen in the other Core Phase 3 studies, the percentage of subjects with a history of CAD is relatively low (8%).

Table 6.9. Baseline Cardiovascular Risk Factors for Subjects in Initial Combination with Metformin Study	
	CV181039 N=1306
History of CAD	8%
History of hypertension	51%
Previous DM treatment	2%
Used baseline CV medication?	48%
HDL cholesterol (mg/dL)	
Mean (SD)	44 (12)
LDL cholesterol (mg/dL)	
Mean (SD)	125 (36)

Source: Individual Clinical Study Report

6.1.3 Patient Disposition

Table 6.10 summarizes the patient disposition for the short-term periods of the Core Phase 3 studies. 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.

Reviewer comment: USA sites constituted 54% of subjects. According to Ms. Mele's review, two major differences were seen between the USA and non-USA sites: 1) an overall higher rescue rate (28%) was seen for the USA sites than the non-USA sites (12%) and 2) for the recommended dose of 5 mg, a higher statistically significant treatment difference favorable to saxagliptin was seen for the USA sites. Because of this, Ms. Mele examined the efficacy data by USA/non-USA sites and looked to ensure that the rescue criteria were applied similarly across sites. To do this, she looked at FPG levels over time for rescued and non-rescued subjects. It appears that subjects in non-USA sites were appropriately rescued when FPG was above the pre-defined FPG rescue criteria.

In addition, Ms. Mele found that baseline values for FPG and BMI for USA sites were higher than for other countries. Therefore it is likely that the differences in rescue seen for the USA sites versus the non-USA sites is based on differences in the populations on important predictors of rescue.

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%)

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	Discontinued for lack of efficacy (excluding rescue) n (%)	Rescued n (%)
	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.

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

Table 6.11 summarizes the patient disposition for the short-term + long-term periods of the Core Phase 3 studies. The percentage of subjects that discontinued study treatment during either the ST or LT period varied. The highest discontinuation was observed in the placebo + metformin group of Study CV181014. For the 120-day safety update data, withdrawal of consent was the most common reason for discontinuation. With the exception of Study CV181039, lack of efficacy was the second most common reason.

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Table 6.11. Disposition of Subjects in the ST + LT Treatment Period of the Core Phase 3 Studies, 120-Day Safety Update				
Population	Treatment Group	Number Randomized and Treated	Number Entered LT Period n (%)	Subjects Discontinued n (%)
Pooled Monotherapy	Saxa 2.5 mg	247	209 (84.6)	125 (50.6)
	Saxa 5 mg	252	213 (84.5)	107 (42.5)
	Saxa 10 mg	98	83 (84.7)	52 (53.1)
	Placebo	169	142 (84.5)	87 (51.5)
CV181014	Saxa 2.5 mg + Met	192	168 (87.5)	100 (52.1)
	Saxa 5 mg + Met	191	162 (84.8)	102 (53.4)
	Saxa 10 mg + Met	181	162 (89.5)	88 (48.6)
	Placebo + Met	179	151 (84.4)	128 (71.5)
CV181040	Saxa 2.5 mg + Gly	248	224 (90.3)	61 (24.6)
	Saxa 5 mg + Gly	253	227 (89.7)	60 (23.7)
	Placebo + Gly	267	235 (88.0)	80 (30.0)
	Saxa 2.5 mg + TZD	195	173 (88.7)	60 (30.8)
CV181013	Saxa 5 mg + TZD	186	150 (80.6)	65 (34.9)
	Placebo + TZD	184	145 (78.8)	73 (39.7)
	Saxa 5mg + Met	320	276 (86.3)	84 (26.3)
	Saxa 10 mg + Met	323	275 (85.1)	77 (23.8)
CV181039	Saxa 10 mg	335	286 (85.4)	116 (34.6)
	Metformin	328	266 (81.1)	95 (29.0)

Source: 120-Day Safety Update, Table 1.4

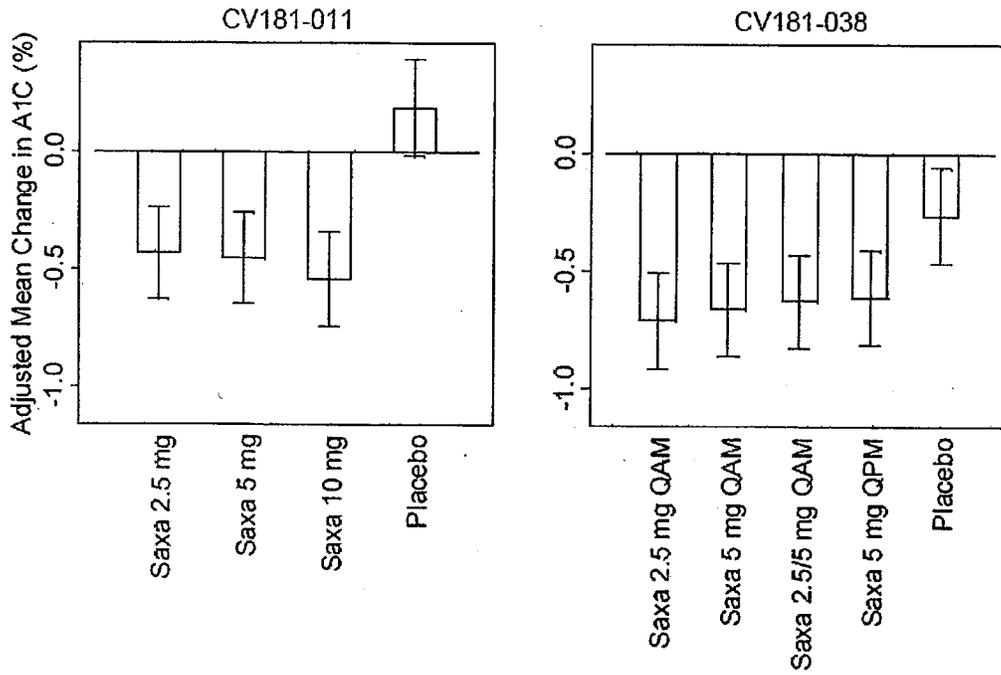
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Table 6.12. Change in HbA1c from baseline at Week 24 (LOCF)--Phase 3 Monotherapy Studies (%)

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181011					
Saxa 2.5mg	100/102	7.91 (0.09)	7.48 (0.11)	-0.43 (0.10)	-0.62 [0.90, 0.33]
Saxa 5mg	103/106	7.98 (0.11)	7.51 (0.13)	-0.46 (0.10)	-0.64 [-0.93, -0.36]
Saxa 10mg	95/98	7.85 (0.09)	7.32 (0.10)	-0.54 (0.10)	-0.73 [-1.02, -0.44]
Placebo	92/95	7.88 (0.10)	8.07 (0.17)	0.19 (0.10)	--
CV181038					
Saxa 2.5mg	67/74	8.04 (0.11)	7.30 (0.11)	-0.71 (0.10)	-0.45 [-0.74, -0.16]
Saxa 5mg QAM	69/74	7.93 (0.11)	7.27 (0.13)	-0.66 (0.10)	-0.40 [-0.69, -0.12]
Saxa 2.5/5mg	69/71	8.02 (0.13)	7.37 (0.14)	-0.63 (0.10)	-0.37 [-0.65, -0.08]
Saxa 5mg QPM	70/72	7.88 (0.11)	7.29 (0.12)	-0.61 (0.10)	-0.35 [-0.63, -0.07]
Placebo	68/74	7.79 (0.11)	7.57 (0.14)	-0.26 (0.10)	--
Pooled Monotherapy					
Pooled Saxa 2.5mg	167/176	7.96 (0.07)	7.40 (0.08)	-0.58 (0.08)	-0.56 [-0.76, -0.35]
Pooled Saxa 5mg	242/252	7.94 (0.06)	7.38 (0.08)	-0.54 (0.06)	-0.52 [-0.71, -0.32]
Pooled Placebo	160/169	7.84 (0.07)	7.86 (0.11)	-0.02 (0.08)	--

Source: Summary of Clinical Efficacy, Table 3.2.2.1A

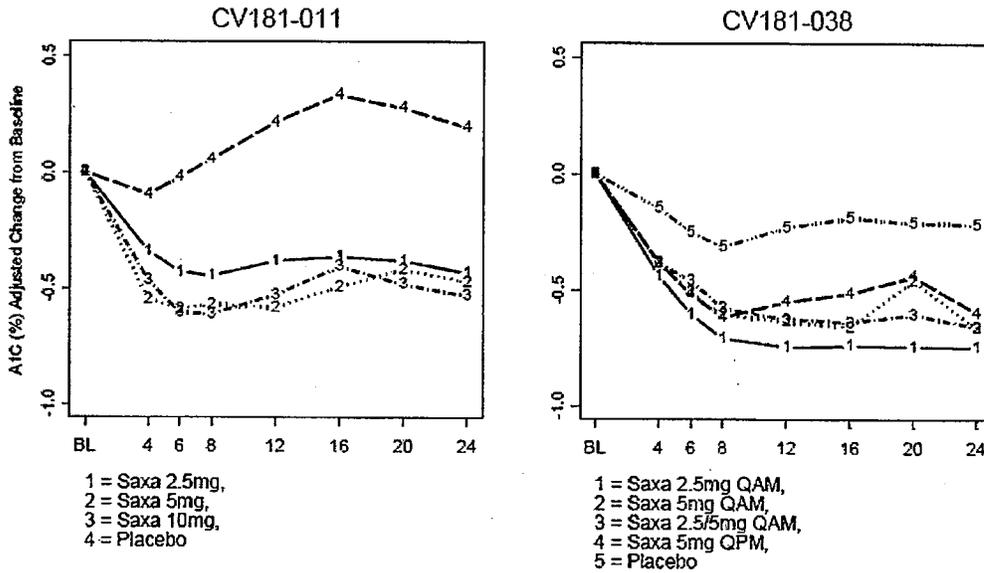
Figure 6.1. HbA1c Adjusted Mean Percent Changes (CI) from Baseline at Week 24 (LOCF)—Phase 3 Monotherapy Studies



Source: Summary of Clinical Efficacy, Figure 3.2.1.1A

Figure 6.2 displays the changes in HbA1c by week in the ST period. In CV181011, reductions in HbA1c were seen by Week 4 in all saxagliptin treatment groups. Major further reductions were not seen at later time points. In Study CV181038, reductions in HbA1c were also seen by Week 4, and most HbA1c lowering had occurred by Week 8.

Figure 6.2. Adjusted Changes from Baseline in HbA1C (LOCF) During ST Period--Phase 3 Monotherapy Studies



Source: Summary of Clinical Efficacy, Figure 3.2.1.1.B

Add-on Combination Studies

Table 6.13 summarizes the changes in HbA1c from baseline to Week 24 for subjects in the add-on combination studies, and these results are represented graphically in Figure 6.3. The decreases in HbA1c observed were statistically significant. In all 3 add-on studies, saxagliptin 5 mg resulted in numerically greater placebo-corrected reductions in A1c compared to the 2.5 mg dose: -0.63% vs. -0.36% for the add-on to TZD study, -0.72% vs. -0.62% for the add-on to glyburide study, and -0.83% vs. -0.73% for the add-on to metformin study. The mean reduction in HbA1c with the 10 mg dose in Study CV181014 was no better than that seen with 2.5 mg.

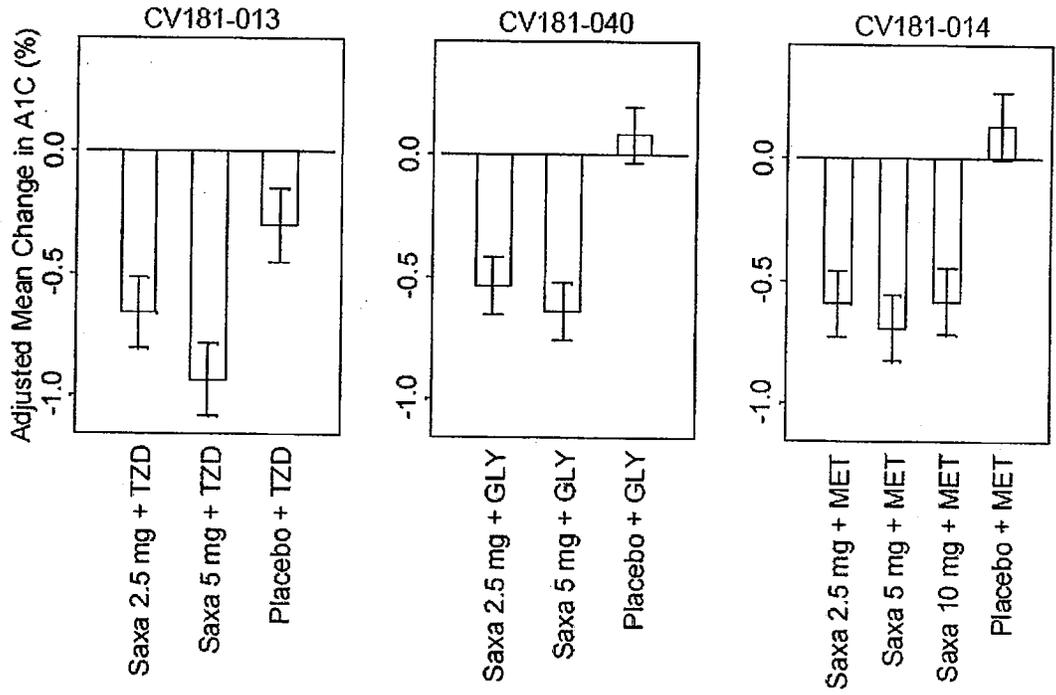
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Table 6.13. HbA1c Changes from Baseline at Week 24 (LOCF)--Phase 3 Add-on Combination Therapy Studies (%)

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181013					
Saxa 2.5mg + TZD	192/195	8.25 (0.080)	7.59 (0.098)	-0.66 (0.074)	-0.36 [-0.57, -0.15]
Saxa 5mg + TZD	183/186	8.35 (0.080)	7.39 (0.086)	-0.94 (0.075)	-0.63 [-0.84, -0.42]
Pla + TZD	180/184	8.19 (0.080)	7.91 (0.100)	-0.30 (0.076)	--
CV181040					
Saxa 2.5mg + Gly	246/248	8.36 (0.057)	7.83 (0.074)	-0.54 (0.059)	-0.62 [-0.78, -0.45]
Saxa 5mg + Gly	250/253	8.48 (0.056)	7.83 (0.074)	-0.64 (0.059)	-0.72 [-0.88, -0.56]
Pla + uptitrated Gly	264/267	8.44 (0.055)	8.52 (0.077)	0.08 (0.057)	--
CV181014					
Saxa 2.5mg + Met	186/192	8.08 (0.07)	7.48 (0.08)	-0.59 (0.07)	-0.73 [-0.92, -0.53]
Saxa 5mg + Met	186/191	8.07 (0.06)	7.37 (0.08)	-0.69 (0.07)	-0.83 [-1.02, -0.63]
Saxa 10mg + Met	180/181	7.98 (0.08)	7.42 (0.09)	-0.58 (0.07)	0.72 [-0.91, -0.52]
Pla + Met	175/179	8.06 (0.07)	8.19 (0.09)	0.13 (0.07)	--

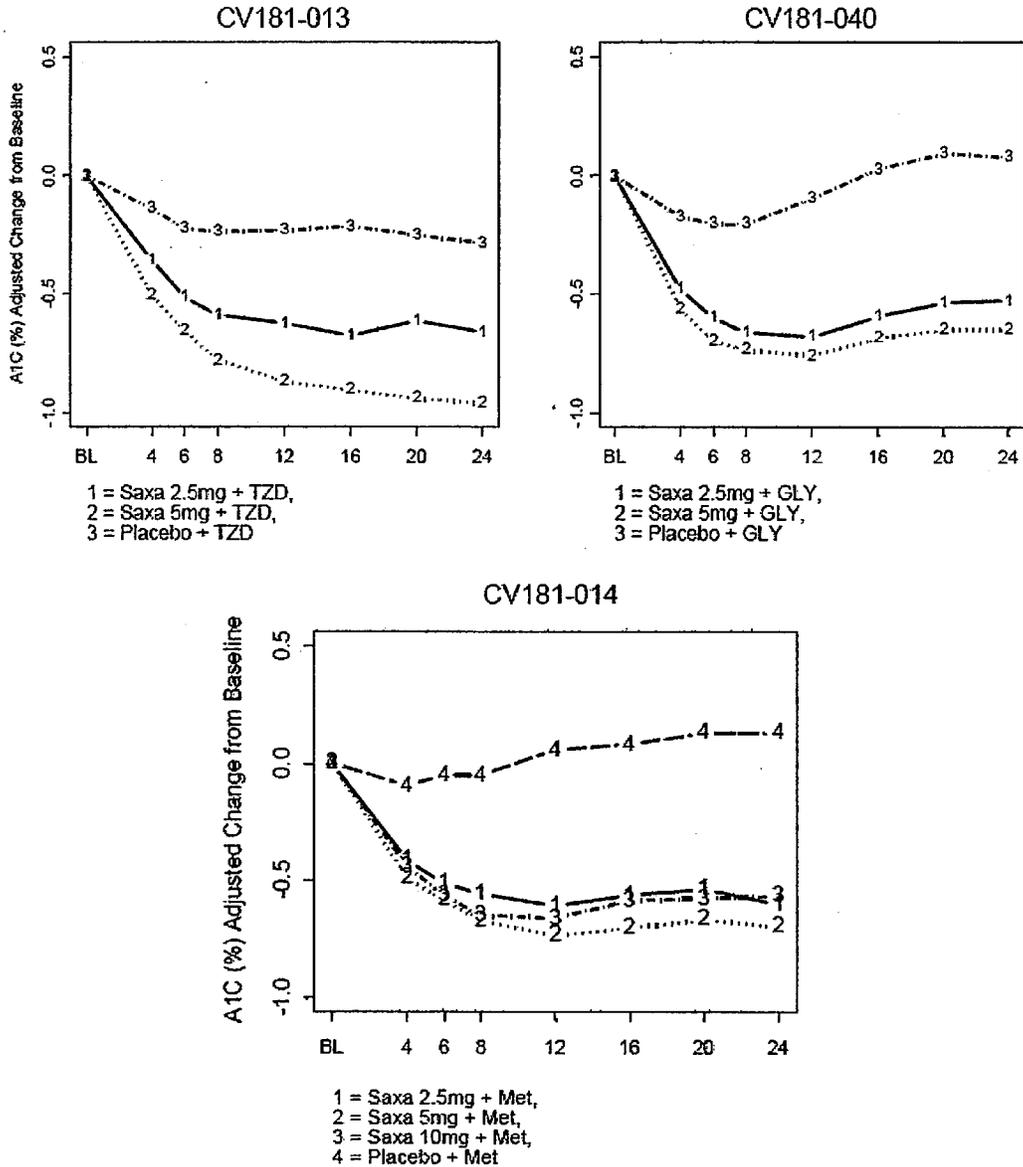
Source: Summary of Clinical Efficacy, Table 3.2.2.1

Figure 6.3. A1c Adjusted Mean Changes from Baseline at Week 24 (LOCF)--Phase 3 Add-on Combination Studies



Source: Summary of Clinical Efficacy, Figure 3.2.2.1A

The figures below display the changes in HbA1c by week in the ST period for the LOCF populations. As seen in the monotherapy studies, decreases in HbA1c were apparent by Week 4. The saxagliptin curves continued their divergence from placebo through Week 24.



Initial Combination Study with Metformin

The saxagliptin 5 mg + metformin and the saxagliptin 10mg + metformin groups both had statistically significant reductions in HbA1c when compared with either monotherapy groups. This is summarized in the table below and graphically displayed in Figure 6.4. The saxagliptin 5 mg + metformin group had the largest numerical reduction in HbA1c from baseline.

6.1.4 Analysis of Primary Endpoint(s)

Monotherapy Studies

Table 6.12 summarizes the changes in HbA1c from baseline to Week 24 for the primary monotherapy populations, and these results are represented graphically in Figures 6.1-6.2. The decreases in HbA1c observed were statistically significant. In these studies, placebo-corrected reductions from baseline in HbA1c ranged from 0.35% to 0.73% from baseline. For the Pooled Monotherapy Analysis, saxagliptin 5 mg lowered HbA1c by 0.54% compared to 0.02% for placebo. Therefore, in the pooled monotherapy trials, mean HbA1c reduction in the saxagliptin 2.5mg and 5mg groups relative to placebo was a modest -0.56% and -0.52%, respectively.

In both monotherapy trials, saxagliptin 2.5 mg and 5 mg resulted in similar placebo-corrected reductions in HbA1c.

In Study CV181038, the largest decrease in HbA1c was seen in the saxagliptin 2.5 mg group. The saxagliptin 5 mg QPM and QAM treatment groups yielded similar results. Also, there did not appear to be any difference in the change from baseline in HbA1c in groups with titration from 2.5 to 5 mg, compared to the fixed dose treatment groups. Of note, the placebo group had an adjusted change from baseline in HbA1c of -0.26%, larger than that seen in the placebo group in Study CV181011. Both studies incorporated diet and exercise instruction according to American Diabetes Association (ADA) or similar local guidelines that were to be followed for the study duration. It is unclear why placebo subjects in CV181038 would be more compliant with these instructions than their placebo counterparts in CV181011. Indeed, weight reductions from baseline to Week 24 were nearly identical in both studies CV181011 and CV181038 (1.35 kg and 1.3 kg, respectively).

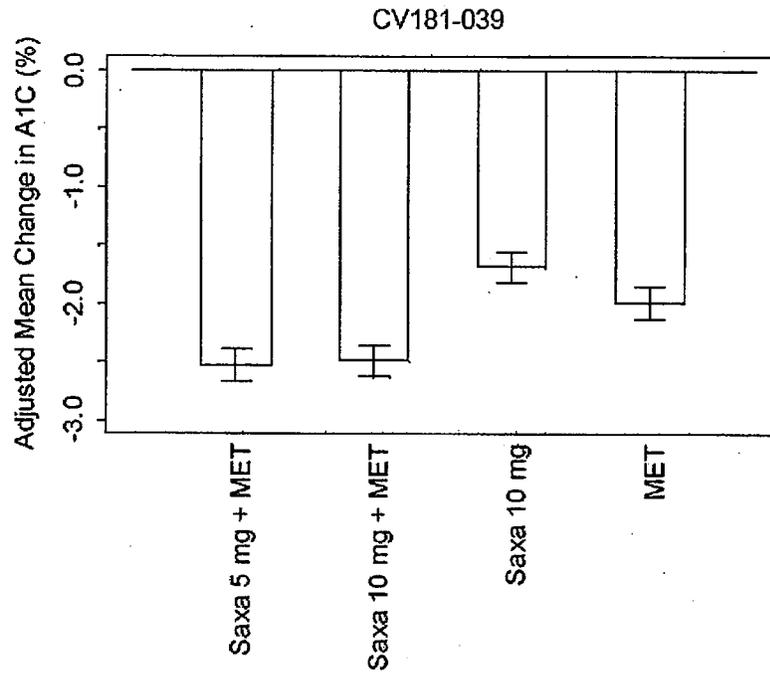
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Table 6.14. HbA1c Change from Baseline at Week 24 (LOCF)--Initial Combination Study (CV1818039)

Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adj. Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
Saxa 5mg + Met	306/320	9.41 (0.072)	6.93 (0.066)	-2.53 (0.070) [-2.66, -2.39]	
vs Saxa 10mg vs Met					-0.84 [-1.03, -0.65] -0.54 [-0.73, -0.35]
Saxa 10mg + Met	315/323	9.53 (0.069)	7.02 (0.067)	-2.49 (0.069) [-2.62, -2.35]	
vs Saxa 10mg vs Met					-0.80 [-0.99, -0.61] -0.50 [-0.70, -0.31]
Saxa 10mg	317/335	9.61 (0.075)	7.86 (0.085)	-1.69 (0.069) [-1.82, -1.55]	--
Metformin	313/328	9.43 (0.073)	7.48 (0.084)	-1.99 (0.069) [-2.12, -1.85]	--

Source: Summary of Clinical Efficacy, Table 3.2.3.1

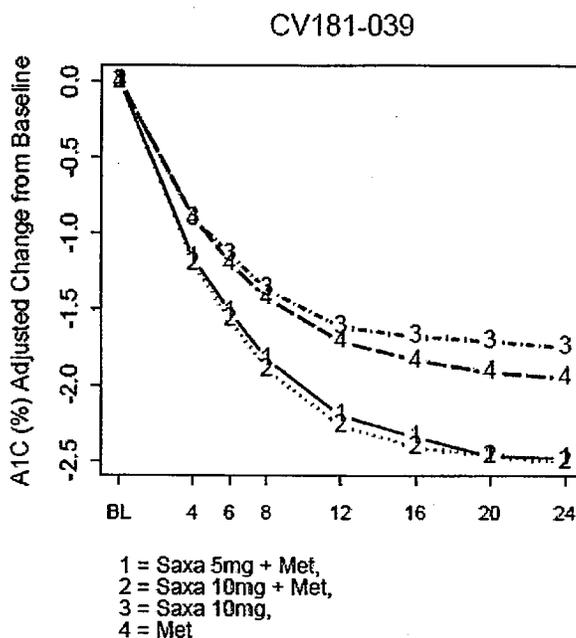
**Figure 6.4. HbA1c Adjusted Mean Changes from Baseline at Week 24 Values (LOCF)—
Initial Combination Study with Metformin**



Source: Summary of Clinical Efficacy, Figure 3.2.3.1A

Figure 6.5 displays the changes in HbA1c by week in the ST period. As seen in the monotherapy and add-on combination studies, decreases in HbA1c were apparent by Week 4. Both curves of the saxagliptin + metformin groups remained diverged from the monotherapy groups through Week 24.

Figure 6.5. Adjusted Changes from Baseline in HbA1c (LOCF) During ST Period-- Initial Combination Study with Metformin



Source: Summary of Clinical Efficacy, Figure 3.2.3.1B

6.1.5 Analysis of Secondary Endpoints(s)

Monotherapy Studies

Fasting plasma glucose (FPG)

Table summarizes the change in fasting plasma glucose (FPG) from baseline to Week 24 in the monotherapy studies. In Study CV181011, statistically significant reductions in FPG were seen across all saxagliptin treatment groups compared with placebo. In Study CV181038, statistically significant reductions were seen only in the AM dosing groups. All reductions were less marked than those observed in Study CV181011. Statistically significant reductions were also seen in the Pooled Monotherapy Analysis. In Study CV181011, the placebo-corrected reduction in FPG was numerically greater with saxagliptin 2.5 mg than with the 5 mg dose. In Study CV181038, both doses resulted in similar placebo-corrected reductions in FPG.

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Table 6.15. Fasting Plasma Glucose Changes from Baseline at Week 24 (LOCF)--Phase 3 Monotherapy Studies

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181011					
Saxa 2.5 mg	101/102	177.72 (4.12)	162.09 (4.58)	-14.53 (3.82)	-20.60 [-31.5, -9.7]
Saxa 5 mg	105/106	171.31 (4.0)	163.64 (5.04)	-8.67 (3.74)	-14.73 [-25.5, -4.0]
Saxa 10 mg	97/98	176.51 (4.43)	159.05 (3.92)	-16.75 (3.89)	-22.81 [-33.8, -11.8]
Placebo	92/95	171.85 (4.80)	178.73 (5.70)	6.06 (4.00)	--
CV181038					
Saxa 2.5 mg	70/74	156.6 (3.96)	146.8 (3.79)	-11.4 (4.50)	-14.7 [-27.2, -2.3]
Saxa 5 mg	71/74	162.2 (4.24)	151.3 (5.88)	-10.7 (4.46)	-14.0 [-26.4, -1.6]
Saxa 2.5/5 mg	71/71	170.6 (6.15)	155.2 (5.88)	-12.5 (4.48)	-15.8 [-28.3, -3.4]
Saxa 5 mg QPM	71/72	159.6 (5.32)	152.4 (5.88)	-7.9 (4.46)	-11.2 [-23.2, 1.2]
Placebo	71/74	158.6 (5.44)	162.9 (6.28)	3.3 (4.46)	--
Pooled Monotherapy					
Pooled Saxa 2.5 mg	171/176	169.09 (3.03)	155.84 (3.16)	-12.85 (3.05)	-18.15 [-216.7, -9.61]
Pooled Saxa 5 mg	247/252	165.33 (2.63)	156.85 (3.22)	-8.59 (2.54)	-13.89 [-21.8, -5.97]
Pooled Placebo	163/169	166.07 (3.63)	171.82 (4.26)	5.30 (3.12)	--

Source: Summary of Clinical Efficacy, Table 3.2.1.2A

A1c<7%

A therapeutic glycemc response was defined as achieving A1c<7% at Week 24 (LOCF). In Study CV181011, a statistically significantly greater proportion of subjects met this criterion in the saxagliptin 5 mg and 10 mg groups compared with placebo; the results for the 2.5 mg group were not statistically significant.

Reviewer comment: Despite the statistically significant results, these are considered exploratory because of multiple comparisons and no control of the type 1 error rate.

In Study CV181038, results were not statistically significant across all treatment groups. In the Pooled Monotherapy Analysis, statistically significant results were achieved in the 5 mg group, with approximately 40% of subjects achieving this criterion compared with approximately 29% of placebo subjects.

Table 6.16. Percent of Subjects Achieving Therapeutic Glycemic Response (A1c<7%) at Week 24 (LOCF)—Phase 3 Monotherapy Studies			
Study/Treatment	n/N	Number (%) of Subjects Achieving A1c<7%	Difference from Control [95% CI]
CV181011			
Saxa 2.5 mg	100/102	35 (35.0)	11.1 [-3.1, 24.9]
Saxa 5 mg	103/106	39 (37.9)	14.0 [-0.1, 27.6]
Saxa 10 mg	95/98	39 (41.1)	17.1 [2.8, 31.0]
Placebo	92/95	22 (23.9)	3.3 [-12.9, 19.5]
CV181038			
Saxa 2.5 mg	67/74	24 (35.8)	0.5 [-15.9, 16.7]
Saxa 5 mg	69/74	31 (44.9)	9.6 [-7.1, 25.8]
Saxa 2.5/5 mg	69/71	30 (43.5)	8.2 [-8.5, 24.3]
Saxa 5 mg QPM	70/72	27 (28.6)	3.3 [-12.9, 19.5]
Placebo	68/74	24 (35.3)	--
Pooled Monotherapy			
Pooled Saxa 2.5 mg	167/176	59 (35.3)	6.58 [-3.60, 16.64]
Pooled Saxa 5 mg	242/252	97 (40.1)	11.33 [1.74, 20.48]
Pooled Placebo	160/169	46 (28.8)	--

Source: Summary of Clinical Efficacy, Table 3.2.1.2C

Post-prandial glucose (PPG)

In Study CV181011, statistically significant reductions in PPG AUC were seen in the saxagliptin 2.5 mg, 5 mg and 10 mg groups compared to placebo.

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In Study CV181038, the differences in mean reductions were only nominally significant for the saxagliptin QAM treatment groups. For the Pooled Monotherapy population, decreases from baseline to Week 24 in PPG AUC in the 2.5 mg and 5 mg groups were greater than the placebo group (statistically significant).

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Table 6.17. Postprandial Glucose AUC Changes from Baseline at Week 24 (LOCF)--Phase 3 Monotherapy Studies (unit: mg*min/dL)

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181011					
Saxa 2.5 mg	74/102	45030 (1368.1)	38323 (1239.1)	-6868 (1167.7)	-6221 [-9570, -2872]
Saxa 5 mg	79/106	45691 (1209.8)	38604 (1352.0)	-6896 (1130.2)	-6249 [-9546, -2952]
Saxa 10 mg	73/98	44614 (1394.0)	36912 (1155.8)	-8084 (1176.2)	-7437 [-10798, -4076]
Placebo	66/95	46030 (1397.8)	45011 (1574.2)	-646.6 (1236.9)	--
CV181038					
Saxa 2.5 mg	48/74	47432 (1496.6)	39798 (1347.0)	-8014 (1246.9)	-4927 [-8416, -1437]
Saxa 5 mg	48/74	50417 (1561.5)	41562 (1489.3)	-8218 (1249.1)	-5130 [-8630, -1630]
Saxa 2.5/5 mg	47/71	50032 (1684.7)	41745 (1739.2)	-7781 (1261.0)	-4694 [-8210, -1178]
Saxa 5 mg QPM	43/72	47078 (1941.9)	41530 (1962.7)	-6048 (1318.2)	-2961 [-6650, 629]
Placebo	47/74	47640 (1759.7)	44861 (1854.7)	-3088 (1259.7)	--
Pooled Monotherapy					
Pooled Saxa 2.5 mg	122/176	45975 (1019.1)	38903 (918.4)	-7392 (883.3)	-5634 [-8121, -3147]
Pooled Saxa 5 mg	170/252	47376 (875.1)	40179 (906.2)	-6937 (744.0)	-5179 [-7501, -2856]
Pooled Placebo	113/169	46700 (1094.0)	44949 (1194.8)	-1758 (914.8)	--

Source: Summary of Clinical Efficacy, Table 3.2.1.2D

Add-on Combination Studies

Fasting plasma glucose (FPG)

All observed placebo-corrected reductions in FPG were statistically significant. Overall, the greatest decreases were seen in the saxagliptin treatment groups in Study CV181014 and the smallest reductions were seen in the saxagliptin treatment groups in Study CV181040. Across all studies, the greatest mean reductions in FPG were in the saxagliptin 5 mg add-on therapy groups, although differences from the 2.5 mg dose groups were small. In Study CV181014, the saxagliptin 10 mg group did not achieve a better placebo-corrected reduction in FPG compared to the 5 mg group.

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Table 6.18. Fasting Plasma Glucose Changes from Baseline at Week 24 (LOCF)--Phase 3 Add-on Combination Studies

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95%CI]
CV181013					
Saxa 2.5 mg + TZD	193/195	163.0 (3.54)	148.2 (3.36)	-14.3 (2.87)	-11.6 [-19.7, -3.4]
Saxa 5 mg + TZD	185/186	159.5 (3.34)	143.0 (3.20)	-17.3 (2.94)	-14.5 [-22.7, -6.3]
Placebo + TZD	181/184	162.4 (3.43)	159.3 (4.29)	-2.8 (2.97)	--
CV181040					
Saxa 2.5 mg + Gly	247/248	170.1 (2.67)	164.4 (2.76)	-7.1 (2.42)	-7.7 [-14.3, -1.1]
Saxa 5 mg + Gly	253/253	175.0 (2.79)	164.6 (2.76)	-9.7 (2.39)	-10.3 [-16.9, -3.8]
Placebo + titrated Gly	265/267	174.4 (2.64)	174.6 (2.93)	0.7 (2.33)	--
CV181014					
Saxa 2.5 mg + Met	188/192	173.6 (3.23)	159.9 (3.25)	-14.31 (2.48)	-15.55 [-22.6, -8.6]
Saxa 5 mg + Met	187/191	179.0 (3.44)	156.1 (3.11)	-22.03 (2.49)	-23.28 [-30.3, -16.3]
Saxa 10 mg + Met	181/181	175.9 (3.73)	155.4 (3.75)	-20.50 (2.53)	-21.74 [-28.8, -14.7]
Placebo + Met	176/179	174.9 (3.27)	176.5 (3.86)	1.24 (2.56)	--

Source: Summary of Clinical Efficacy, Table 3.2.2.24

A1c<7%

In all of the add-on combination studies, a statistically significantly higher proportion of saxagliptin-treated subjects achieved the pre-specified therapeutic glycemic response, compared to placebo add-on therapy or uptitrated glyburide groups. The 2.5 mg and 5 mg dose groups had similar responses, except perhaps in Study CV181014. As seen with the other efficacy parameters, the saxagliptin 10 mg dose in Study CV181014 did not confer additional efficacy compared to the saxagliptin 5 mg dose with regard to the proportion of patients achieving therapeutic glycemic response.

Table 6.19. Percent of Subjects Achieving Therapeutic Glycemic Response (A1c<7%) at Week 24 (LOCF)--Phase 3 Add-on Combination Therapy Studies (unit: %)			
Study/Treatment	n/N	Number (%) of Subjects Achieving A1c<7%	Difference from Control [95% CI]
CV181013			
Saxa 2.5 mg + TZD	192/195	81 (42.2)	16.6 [7.0, 26.0]
Saxa 5 mg + TZD	184/186	77 (41.8)	16.3 [6.5, 25.7]
Placebo + TZD	180/184	46 (25.6)	--
CV181040			
Saxa 2.5 mg + Gly	246/248	55 (22.4)	13.3 [7.1, 19.7]
Saxa 5 mg + Gly	250/253	57 (22.8)	13.7 [7.5, 20.1]
Placebo + titrated Gly	264/267	24 (9.1)	--
CV181014			
Saxa 2.5 mg + Met	186/192	69 (37.1)	20.5 [10.6, 30.5]
Saxa 5 mg + Met	186/191	81 (43.5)	27.0 [17.0, 36.7]
Saxa 10 mg + Met	180/181	80 (44.4)	27.9 [17.7, 37.7]
Placebo + Met	175/179	29 (16.6)	--

Source: Summary of Clinical Efficacy, Table 3.2.2.2B

Post-prandial glucose (PPG)

Statistically significant decreases from baseline to Week 24 in postprandial glucose AUC were seen in all saxagliptin add-on therapy treatment groups compared with placebo. These data are summarized below. The response with the 10 mg dose in Study CV181014 was no better than that seen with the 2.5 mg dose.

Table 6.20. Postprandial Glucose AUC Changes from Baseline at Week 24 (LOCF)--Phase 3 Add-on Combination Therapy Studies

Study/Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
CV181013					
Saxa 2.5 mg + TZD	151/195	48301 (968.5)	40255 (919.7)	-7849 (740.6)	-5159 [-7333, -2985]
Saxa 5 mg + TZD	131/186	47866 (1048.9)	38587 (991.3)	-9269 (794.9)	-6579 [-8826, -4333]
Placebo + TZD	123/184	47256 (1057.4)	44819 (1023.4)	-2690 (820.6)	--
CV181040					
Saxa 2.5 mg + Gly	190/248	49124 (677.2)	45402 (681.5)	-4296 (595.0)	-5492 [-7122, -3862]
Saxa 5 mg + Gly	195/253	50342 (669.0)	45391 (699.3)	-5000 (585.5)	-6195 [-7807, -4584]
Placebo + uptitrated Gly	204/267	51801 (656.9)	52416 (703.7)	1196 (574.5)	--
CV181014					
Saxa 2.5 mg + Met	150/192	48224 (869.7)	38880 (912.0)	-8891 (798.0)	-5599 [-7894, -3305]
Saxa 5 mg + Met	146/191	49021 (876.2)	38548 (850.5)	-9586 (810.5)	-6294 [-8606, -3983]
Saxa 10 mg + Met	148/181	44931 (889.9)	38137 (925.6)	-8137 (807.9)	-4845 [-7153, -2537]
Placebo + Met	131/179	47407 (1071.9)	44108 (977.8)	-3291 (853.2)	--

Source: Summary of Clinical Efficacy, Table 3.2.2.2C

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Initial Combination Study with Metformin

Fasting plasma glucose (FPG)

Reductions seen in both saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups were statistically significant. The saxagliptin 10 mg + metformin group had the highest numerical reduction in FPG from baseline.

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Table 6.21. Fasting Plasma Glucose Changes from Baseline at Week 24 (LOCF)--Phase 3 Initial Combination Study						
Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95%CI]	
Saxa 5 mg + Met	315/320	198.9 (3.17)	140.2 (2.39)	-59.8 (2.34) [-64.4, -55.2]		
vs Saxa 10 mg vs Met					-28.9 [-35.3, -22.4] -12.5 [-19.0, -6.0]	
Saxa 10 mg + Met	317/323	204.3 (3.35)	140.1 (2.34)	-62.2 (2.34) [-66.8, -57.7]		
vs Saxa 10 mg vs Met					-31.3 [-37.7, -24.9] -14.9 [-21.4, -8.5]	
Saxa 10 mg	327/335	200.9 (3.03)	169.9 (3.20)	-30.9 (2.30) [-35.5, -26.4]	--	
Metformin	320/328	199.1 (3.28)	152.7 (2.80)	-47.3 (2.33) [-51.9, -42.8]	--	

Source: Summary of Clinical Efficacy, Table 3.2.3.2A

A1c<7%

The proportion of subjects with an A1c<7% at Week 24 was greatest for the saxagliptin 5 mg + metformin and the saxagliptin 10 mg + metformin groups compared with either monotherapy group. The data are summarized below.

Table 6.22. Percent of Subjects Achieving Therapeutic Glycemic Response (A1c<7%) at Week 24 (LOCF)--Phase 3 Initial Combination Study			
Study/ Treatment	n/N	Number (%) of Subjects Achieving A1c<7%	Difference from Control [95% CI]
Saxa 5 mg + Met	307/320	185 (60.3)	
vs Saxa 10 mg			28.1 [20.4, 35.4]
vs Met			19.2 [11.3, 26.8]
Saxa 10 mg + met	315/323	188 (59.7)	
vs Saxa 10 mg			27.5 [19.8, 34.8]
vs Met			18.6 [10.8, 26.3]
Saxa 10 mg	320/335	103 (32.2)	--
Metformin	314/328	129 (41.1)	--

Source: Summary of Clinical Efficacy, Table 3.2.3.2B

Post-prandial glucose (PPG)

The saxagliptin 5 mg + metformin and saxagliptin 10 mg + metformin groups had statistically significant reductions from baseline to Week 24 in PPG AUC when compared with either monotherapy group. The saxagliptin 10 mg + metformin group had the largest reduction from baseline. The results are summarized below.

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Table 6.23. Postprandial Glucose AUC Changes from Baseline to Week 24 (LOCF) in Study CV81039

Study/ Treatment	n/N	Baseline Mean (SE)	Week 24 Mean (SE)	Adjusted Mean Change from Baseline (SE)	Difference from Control in Adjusted Mean Change from Baseline [95% CI]
Saxa 5 mg + Met	142/320	5531 (1116.5)	35324 (890.0)	-21080 (836.5) [-22723, -19437]	
vs Saxa 10 mg vs Met					-5027 [-7338, -2715] -6075 [-8429, -3271]
Saxa 10 mg + met	131/323	57219 (1169.6)	35790 (888.9)	-213336 (869.6) [-23044, -19628]	
vs Saxa 10 mg vs Met					-5282 [-7639, -2925] -6330 [-8728, -3932]
Saxa 10 mg	145/335	57584 (1143.4)	41229 (1050.9)	-16054 (826.7) [-17677, -14430]	--
Metformin	135/328	57937 (1281.7)	42428 (1082.1)	-15005 (857.0) [-166889, -13322]	--

Source: Summary of Clinical Efficacy, Table 3.2.3.2A

6.1.6 Other Endpoints

Other efficacy endpoints measured by the Sponsor included:

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-
-
-

b(4)

However, these endpoints are considered exploratory and will not be included in labeling and therefore results are not presented here.

6.1.7 Subpopulations

The Sponsor performed analyses of the effect of saxagliptin on HbA1c in 12 clinical subgroup categories of potential interest. Some of these, including baseline HbA1c, race, baseline creatinine clearance, gender, age, and baseline BMI, are presented in this Section. The Sponsor specifically sought to examine whether saxagliptin is ineffective in certain populations. Overall the point estimates showed that saxagliptin reduced A1c in all subgroups, with the exception of 12 subgroups out of more than 500 comparisons. It should be noted that the Sponsor did not design the studies to adequately power for subgroup analysis of A1c reduction. Nevertheless, the 95% CI for the placebo-corrected or active-control corrected adjusted mean reduction in A1c excluded zero in most subgroups. Of the 12 exceptions mentioned above, 9 were derived from the CV181038 trial, which had the smallest numbers per treatment group (including 8 subgroups which had a sample size of ≤ 8).

Formal treatment-by-subgroup interaction testing was used to evaluate subgroups where the effect of saxagliptin varied. Results of these tests are presented below. The p-values represent all treatment groups in the analysis of each study, and the pooled analyses contain only the saxagliptin 2.5 mg and 5 mg and placebo groups. Those treatment-by-subgroup interactions with a p-value < 0.1 indicate a potential signal. These are in bold in the Table below. No subgroup category generated an interaction p-value < 0.1 in more than 3 of the individual studies.

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Table 6.24. Subgroup Interaction p-values for the Comparison in A1c at Week 24 (LOCF)--Core Phase 3 Studies

	CV181011	CV181038	CV181013	CV181040	CV181014	CV181039	No. Positive	Pooled Mono-therapy	Pooled Mono-therapy/Add-on
Baseline A1c	0.0222	0.6062	0.0492	0.5907	0.0308	0.2508	3	0.0137	0.0019
Race	0.0111	0.0742	0.4645	0.5783	0.9188	0.0055	3	0.0992	0.0837
Baseline Creatinine Clearance	0.7760	0.7304	0.2494	0.0550	0.0614	0.7548	2	0.9269	0.0123
Gender	0.0027	0.7738	0.1992	0.9560	0.7250	0.4463	1	0.0085	0.0468
Age	0.9631	0.7011	0.4601	0.5930	0.4955	0.1364	0	0.7684	0.8796
Baseline BMI	0.9121	0.8141	0.4455	0.1805	0.5966	0.1638	0	0.8569	--

Source: Summary of Clinical Efficacy, Table 3.3A