BRISTOL-MYERS SQUIBB COMPANY

SAXAGLIPTIN (BMS-477118)
MODULE 2.5
CLINICAL OVERVIEW

Indication: Type 2 Diabetes Mellitus

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LIST OF ABBREVIATIONS

Abbreviation	Definition
A1C	glycosylated hemoglobin
AE	adverse event
ALT	alanine aminotransferase
AUC	area under plasma concentration-time curve from zero to infinity [amount•time/volume]
AZ	AstraZeneca
BMS	Bristol-Myers Squibb
BCS	Biopharmaceutics Classification System
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CK	creatine kinase
Cmax	maximum plasma (peak) drug concentration after single dose administration [amount/volume]
CrCl	creatinine clearance
CRF	case report form
CYP3A4/5	cytochrome P450 3A4/5
DMC	Data Monitoring Committee
DPP4	dipeptidyl peptidase 4
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GIP	glucose dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
LOCF	last observation carried forward
NOEL	no-observable-effect level
NYHA	New York Heart Association
OGTT	oral glucose tolerance test
PPAR	peroxisome proliferator-activated receptor
PPG	post prandial glucose
PT	preferred term
QD	once daily

Abbreviation	Definition
QTc	corrected QT interval
SAWP	Scientific Advice Working Party
SU	sulfonylurea
SOC	system organ class
T2DM	type 2 diabetes mellitus
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	upper limit of normal

1 PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

Saxagliptin is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[1]. Incretin hormones are gastrointestinal hormones that increase insulin secretion in response to enteral stimulation. These hormones contribute to the control of postprandial glucose excursions in a glucose dependent manner, which mitigates the risk of hypoglycemia. In addition to enhanced postprandial insulin release, GLP-1 also reduces glucagon release from the pancreatic α-cells, thereby reducing hepatic glucose production.[2] This effect is also glucose-dependent, such that when plasma glucose is normal or low, the counter-regulatory response of glucagon release is not impaired.[3]

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disorder that can lead to substantial morbidity and increased mortality rates. Data from the Diabetes Control and Complications Trial[4] (in type 1 diabetes) and the United Kingdom Prospective Diabetes Study[5] (in type 2 diabetes) compared intensive with standard glucose management and showed a reduced risk of complications with improved glucose control as measured by glycosylated hemoglobin (A1C). These results have established tight glucose control as a fundamental component in the management of diabetes. In spite of the availability of a number of different antihyperglycemic classes of agents, achievement of A1C targets remains suboptimal.[6] Many available treatments are associated with undesirable side effects including increased risk of hypoglycemia, weight gain, or edema, which present barriers to their use and acceptance. As a consequence, there remains the need to identify additional effective, safe, and well-tolerated antihyperglycemic agents to help patients achieve and sustain target glycemic levels.

Saxagliptin is intended to improve glycemic control for patients with T2DM:

- as monotherapy as an adjunct to diet and exercise;

- 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 with metformin, as an adjunct to diet and exercise, when treatment with dual saxagliptin and metformin therapy is appropriate.

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

1.2 Overview of Clinical Development Program

1.2.1 Overview

All studies described in this document were performed in accordance with the principles of Good Clinical Practice (GCP). The saxagliptin clinical program is considered concordant with EU and US guidelines on developing treatments for T2DM. [7,8]

The Clinical Pharmacology program consisted of 24 studies in 673 subjects, 620 of whom were dosed with saxagliptin (see Table 1 and Table 2 in Module 2.7.2).[9] Ascending dose studies, biopharmaceutical studies, a thorough corrected QT interval (QTc) study, and studies to investigate various clinical findings were conducted. Drug-drug interactions with saxagliptin and other antihyperglycemic agents, drug metabolizing enzyme inhibitors and probe drugs, as well as with other drugs commonly used in this patient population were evaluated. The pharmacokinetics of saxagliptin was assessed in relation to age, gender, hepatic impairment, and renal impairment, and several studies have investigated the pharmacokinetics of saxagliptin delivered in various formulations. In addition, a population pharmacokinetic analysis was performed.

1.2.2 Phase 3 Dose Evaluation

In the Phase 3 program, saxagliptin doses of 2.5, 5, and 10 mg administered once daily were evaluated to fully characterize the efficacy, safety, and benefit/risk profile of saxagliptin within the dose-response range established in Phase 2. In addition, the potential usefulness of titration of saxagliptin as monotherapy, using a starting dose of

2.5 mg, was examined. The rationale for selecting the dose range and dosing interval for Phase 3 was based on an integrated assessment of efficacy, pharmacodynamic, and safety data generated from subjects exposed to saxagliptin in Phase 1 and 2b studies. The main conclusions from the integrated assessment were the following:

- The largest effect on glycemic control was generally seen at a dose of 5 or 10 mg, with no apparent increase in efficacy at doses higher than 10 mg.
- The largest effect to inhibit plasma DPP4 at trough was seen at a dose of 10 mg, with no apparent increase in inhibition at doses higher than 10 mg.
- Significant inhibition of plasma DPP4 activity was seen at the trough of the dosing interval, ie, 24 hours after dosing of saxagliptin 2.5, 5, and 10 mg.
- Saxagliptin doses in the range of 2.5 to 10 mg were associated with potentiation of postprandial GLP-1 and reduction in excursion of postprandial glucagon.
- Dose-related reduction of absolute lymphocyte count was observed that was most apparent at doses of saxagliptin greater than or equal to 20 mg.

The saxagliptin 5 mg dose was generally associated with maximal efficacy in the Phase 2b study, with no improvement in efficacy at 10 mg. Thus, saxagliptin 5 mg served as the anchor dose in the Phase 3 program. The saxagliptin 10 mg dose was studied to provide additional safety information at a higher dose and to assess whether incremental efficacy of a higher dose would be observed during long-term treatment beyond 12 weeks or in other settings besides monotherapy. The saxagliptin 2.5 mg dose was included to explore the lower end of the dose range. Strict rescue criteria were incorporated in the Core Phase 3 studies to permit additional glucose lowering treatment in the event that subjects experienced poor glycemic control as the clinical studies progressed.

1.2.3 Phase 2b and 3 Clinical Development Program

The Phase 2b and Phase 3 worldwide clinical development program in T2DM included eight studies in which 4607 subjects were randomized and treated. Of these, 3356 subjects received double-blind saxagliptin (Table 1.2.3); an additional 66 subjects received open-label saxagliptin 10 mg in Study CV181011. A total of 1459 subjects received saxagliptin for more than 48 weeks, including 344 who received saxagliptin 10 mg, twice the recommended usual clinical dose (Table 1.2.3A of Module 2.7.4).[10] The eight Phase 2b/3 studies included one 12-week Phase 2b dose-finding study[11], one 12-

week Phase 3 mechanism of action study[12], and six Phase 3 studies with final data from the 24-week short-term treatment period. In the six Phase 3 studies (referred to as the Core Phase 3 studies), 4148 subjects with T2DM were randomized and received study drug, 3021 of whom were treated with saxagliptin. All controlled studies in subjects with T2DM used a randomized, double-blind design.

Interim long-term data from the Phase 3 studies are also included in the submission.

Table 1.2.3: Summary of Controlled Phase 2b-3 Clinical Trials

Study No.	Study objectives (Population)	Randomized and treated subjects All / Saxa	Duration short-term (total)	Saxagliptin (mg) dosage
Monotherapy placebo-controlled				
CV181008	Dose-ranging safety and efficacy (A1C 6.8%-9.7%)	423 / 315	12 weeks or 6 weeks	2.5, 5, 10, 20, or 40 QD or 100 QD
CV181011	Safety and efficacy (A1C 7%-10%)	401 / 306*	24 weeks (206 weeks)	2.5, 5, or 10 QD
CV181038	Safety and efficacy (A1C 7%-10%)	365 / 291	24 weeks (76 weeks)	2.5, 5, or 2.5/5 QAM, or 5 QPM
CV181041	Mechanism of action (A1C 6%-8%)	36 / 20	12 weeks (116 weeks)	5 QD
Add-on combination placebo-controlled				
CV181013	Safety and efficacy (A1C 7%-10.5%)	565 / 381	24 weeks (76 weeks)	2.5 or 5 QD (+ TZD)
CV181014	Safety and efficacy (A1C 7%-10%)	743 / 564	24 weeks (206 weeks)	2.5, 5, or 10 QD (+metformin)
CV181040	Safety and efficacy (A1C 7.5%-10%)	768 / 501	24 weeks (76 weeks)	2.5 or 5 QD (+glyburide)
Initial combination active-controlled				
CV181039	Safety and efficacy (A1C 8%-12%)	1306 / 978	24 weeks (76 weeks)	5 or 10 QD (+metformin) or 10 mg QD

* an additional 66 subjects received open-label saxagliptin in Study CV181011
QD = once daily, QAM = once daily in the morning, QPM = once daily in the evening

For the integrated analyses of safety, data from the Phase 3 monotherapy studies CV181011 and CV181038 were pooled. Data from the five placebo-controlled studies CV181011, CV181038, CV181013, CV181014, and CV181040 were also pooled (Pooled Safety Population) to facilitate the recognition of small safety signals, to better understand consistency across the database, to evaluate dose-relationship, and to potentially increase the precision of determining the frequency of adverse events. This analysis was complementary to the analysis of each individual study.

Monotherapy studies CV181011 and CV181038 enrolled drug naive subjects who were randomized to receive saxagliptin monotherapy 2.5 mg, 5 mg, 10 mg (CV181011 only) or placebo once daily in the morning.[13,14] Study CV181038 also included a 5 mg saxagliptin group with evening (PM) dosing as well as a saxagliptin titration group (2.5 to 5 mg). Sixty-six subjects with screening A1C > 10% and ≤ 12% were enrolled into a saxagliptin 10 mg open-label cohort in Study CV181011 (not represented in Table 1.2.3). Subjects randomized to placebo who completed the short-term treatment period without requiring rescue therapy were given double-blind metformin in the long-term periods of both studies.

The add-on combination studies were conducted in subjects who had inadequate glycemic control despite current therapy with SU, metformin, or TZD. In Study CV181040, subjects who had inadequate glycemic control despite current therapy with a submaximal dose of SU were randomized to saxagliptin 2.5 mg or 5 mg or placebo in combination with an intermediate dose of glyburide. In this study, saxagliptin in combination with a fixed, intermediate dose of glyburide was compared with titration to a higher dose of glyburide plus placebo.[15] In all treatment groups, glyburide could be down-titrated once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. In Study CV181014, subjects who had inadequate glycemic control despite current therapy with metformin were randomized to saxagliptin 2.5, 5, or 10 mg, or placebo, in combination with metformin.[16] In Study CV181013, subjects who had inadequate glycemic control despite current therapy with a TZD were randomized to saxagliptin 2.5 mg or 5 mg or placebo, in combination with a TZD.[17]

In Study CV181039, drug naive subjects who had inadequate glycemic control with A1C 8%-12% were randomized to saxagliptin 5 or 10 mg in inital combination with

metformin 500 mg, to saxagliptin 10 mg monotherapy, or to metformin 500 mg monotherapy.[18] In the saxagliptin 5 mg and 10 mg plus metformin groups, and in the metformin alone group, metformin could be titrated upward to a maximum of 2000 mg per day.

These six studies in subjects with T2DM (Core Phase 3 studies) provide the primary data in support of the efficacy and safety of saxagliptin.

The efficacy and safety of saxagliptin was established in a broad range of subjects with T2DM, including subjects who had inadequate glycemic control on diet and exercise alone, or who had inadequate glycemic control on a single oral antihyperglycemic agent (metformin, SU, or a TZD). The populations studied had inadequate glycemic control with mean baseline A1C values across studies ranging from 7.9% to 9.5% (Section 3.1.1.2 of Module 2.7.3).[19] The geographic scope of the program resulted in a diverse population with subjects enrolled from the United States, Canada, Mexico, Europe, Latin America, and Asia. Several subpopulations classified by age, gender, race, and ethnicity were well represented in the clinical program. While only a small number of subjects ≥ 75 years of age at the time of randomization participated in the Core Phase 3 program, amounting to 59 subjects (1.4%) overall, subjects ≥ 65 years of age were well represented in the clinical program, comprising 634 (15.3%) of subjects (see Appendix 3.5 of the Integrated Summary of Efficacy). As the long-term extensions extend to 204 weeks in two ongoing studies, additional experience in subjects ≥ 75 years will become available in the ongoing program. Saxagliptin has not been evaluated in subjects below 18 years of age, in subjects treated with insulin, in immunocompromised individuals (eg, subjects who have undergone organ transplantation or were diagnosed with human immunodeficiency virus), in subjects with congestive heart failure defined as New York Heart Association (NYHA) stage III and IV and/or known left ventricular ejection fraction of ≤ 40%, or in pregnant or lactating women. Saxagliptin, in repeated dosing, has not been studied in subjects with clinical evidence of active liver disease or with alanine aminotransferase (ALT) > 2 times the upper limit of normal (ULN), in subjects with severe and end-stage renal disease, or in subjects receiving potent CYP3A4 inhibitor or inducer agents.

The quality of data collected and analyzed was monitored according to the Sponsor's Standard Operating Procedures. Issues that might have affected data quality or study conduct were dealt with appropriately. Two primary issues that potentially could have affected data quality are described below along with their resolution.

1) Glucose in excess of the intended 75 g dose was ingested in a number of oral glucose tolerance tests (OGTTs) in Studies CV181038, CV181039, and CV181040. Data from these OGTT procedures, affecting a total of 382 subjects, were excluded from the efficacy analyses. This error primarily impacted the efficacy results in Study CV181038 by further reducing the sample size in this relatively small study.
2) Because of 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 investigative sites in Russia. This situation affected Studies CV181038 and CV181039. For the laboratory parameters used in efficacy analyses, the samples were frozen during the export suspension and held for subsequent analysis at the central laboratory. Hence, any efficacy laboratory parameter analyzed at the emergency central laboratory was not utilized in the statistical efficacy analyses; only results from samples analyzed at the protocol specified central laboratory were utilized. Therefore, this local suspension of lab shipments had no impact on the efficacy results of the studies. For hematology and urinalysis parameters, the values obtained from the emergency central laboratory were used in analysis. The conditions for use of these values and the need for sensitivity analyses on these parameters based on the number of specimens analyzed at the emergency central laboratory were pre-specified in the study Statistical Analysis Plans.

1.2.4 Ongoing Studies

Three Phase 3b studies of saxagliptin in T2DM have recently been initiated (Table 1.2.4). No data are available for inclusion in the current submission.

Table 1.2.4: Summary of Ongoing Clinical Trials in Type 2 Diabetes

Study No.	Study objective (Population)	Randomized and treated subjects (planned) All / Saxa	Duration short-term (total)	Saxagliptin (mg) dosage
CV181054 / D1680C00001	Safety and efficacy of saxagliptin in combination with metformin compared with SU in combination with metformin (A1C 6.5%-10%)	838 / 419	52 weeks (104 weeks)	5 mg (+ metformin IR)

Study No.	Study objective (Population)	Randomized and treated subjects (planned) All / Saxa	Duration short-term (total)	Saxagliptin (mg) dosage
CV181056 / D1680C00002	Safety and efficacy of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin (A1C 6.5%-10%)	710 / 355	18 weeks	5 mg (+ metformin IR)
CV181062 / D1680C00007	Effect of saxagliptin compared with placebo in adult patients with T2DM and renal impairment (moderate, severe, and end-stage) (A1C 7%-10%)	168 / 84	12 weeks (52 weeks)	2.5 mg (+ background medication)

1.3 Overview of Health Authority Interactions

Key health authority interactions that impacted the saxagliptin clinical development program are summarized in this section.

At the US Food and Drug Administration (FDA) End-of-Phase 2 meeting (July 2005), agreements were reached on the overall exposure in the clinical development program, on the designs of the clinical trials to support intended indications, on the clinical pharmacology program, and on the nonclinical toxicology program.[20] Comments were received on the design of the initial combination study (CV181039); a revised study design was approved by the US FDA in February 2006.

In November 2005, the US FDA informed Sponsors developing DPP4 inhibitors that as a class, administration of DPP4 inhibitors to monkeys was associated with dose and duration-dependent necrotizing cutaneous lesions.[21] In February 2007, the US FDA informed Sponsors developing DPP4 inhibitors that although the necrotizing cutaneous lesions had not been observed in humans, symptomatic edema of the hands/feet and laboratory abnormalities had been observed in human subjects.[22] The US FDA advised all Sponsors that subjects should be closely monitored for similar, potentially drug related, findings. Bristol-Myers Squibb (BMS) and AstraZeneca (AZ) developed additional case report forms to monitor events of special interest (skin lesions, selected

infections, lymphopenia, thrombocytopenia, and localized edema), that were submitted and approved by the US FDA.[23,24]

The saxagliptin clinical program was reviewed by the Committee for Medicinal Products for Human Use (CHMP) through the Scientific Advice Procedure. A Discussion Meeting was held on February 26, 2007 and Final Written Advice was received March 22, 2007. The CHMP Scientific Advice Working Party (SAWP) provided feedback on the design of an add-on active-controlled study. This study, D1680C00001 / CV181054, is currently ongoing and is generally concordant with CHMP SAWP Advice. In addition, CHMP SAWP commented on study designs for the ongoing studies CV181013, CV181039, and CV181040. Finally, CHMP SAWP commented that the current safety-handling plan implemented in Phase 3 was thorough and adequate.

The format and content of the US NDA was agreed at the US FDA pre-NDA meeting (November 2007), and the agreement on the exposure by indication was refined.[25]

2 OVERVIEW OF BIOPHARMACEUTICS

Saxagliptin is a Biopharmaceutics Classification System (BCS) Class III compound (high solubility, low permeability based on Caco-2 and Parallel Artificial Membrane Permeability Assay intrinsic permeability assay data),[26,27,28] but it is well absorbed in humans (at least 75%),[29] suggesting it is a borderline BCS Class I compound (high solubility/high permeability). Biopharmaceutics studies in the saxagliptin program examined the relative bioavailability of the capsule formulations used until the end of Phase 2b compared to the Phase 3 tablet formulations. In general, the tablet formulation had earlier and slightly higher maximum plasma concentration (Cmax) values for saxagliptin compared to the capsule formulation, but the overall absorption was the same from both formulations and the degree of DPP4 inhibition provided by each of the formulations was similar (see Module 2.7.1 for a summary of the studies).[30] There were no pivotal bioequivalence studies in the biopharmaceutics clinical pharmacology program since the Phase 3 tablet formulation is very similar to the proposed marketed formulation, differing only in color and embossing with the tablet strength and product code.

Administration of 10 mg saxagliptin in the clinical tablet formulation with a high-fat meal resulted in no change in saxagliptin Cmax and a 27% increase in area under the plasma concentration-time curve (AUC) compared with the fasted state.[31] These changes are not clinically meaningful, and saxagliptin is proposed to be administered without regard to food.

3 OVERVIEW OF CLINICAL PHARMACOLOGY

3.1 Pharmacokinetics

The pharmacokinetics of saxagliptin and its major metabolite, BMS-510849, have been well characterized (see Module 2.7.2).[9] Saxagliptin was rapidly absorbed after oral administration, with maximum plasma concentrations usually attained within 2 hours after dosing. Mass balance and metabolic profiling data suggested that saxagliptin is completely absorbed following an oral dose in humans. Saxagliptin is eliminated via both metabolic and renal pathways, while renal excretion is the primary elimination pathway for BMS-510849. Based on their renal clearance values, saxagliptin renal elimination occurs via a combination of glomerular filtration and net tubular secretion, whereas BMS-510849 appears to be only filtered.

Saxagliptin was metabolized primarily by cytochrome P450 3A4/3A5 (CYP3A) to an active major metabolite, BMS-510849. BMS-510849 was also demonstrated to be a reversible, selective, competitive DPP4 inhibitor, half as potent as saxagliptin. Systemic exposure values for the metabolite were between 2- and 7-times higher than those of saxagliptin.

Plasma exposure for saxagliptin and BMS-510849 increased in proportion with the saxagliptin dose over and beyond the saxagliptin therapeutic dose range. No appreciable accumulation was observed upon repeated once-daily dosing at any dose up to 400 mg once daily (QD). No dose- and time-dependency was observed in saxagliptin clearance over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg. Food had no meaningful effect on saxagliptin pharmacokinetics.

3.1.1 Drug-Drug Interactions

No clinically meaningful drug-drug interaction has been identified in the saxagliptin clinical development program (Section 2.4 of Module 2.7.2).[9]

The in vitro protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Therefore, the propensity of saxagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

Saxagliptin and BMS-510849 neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4 in vitro. Therefore, saxagliptin and its major metabolite are unlikely to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes.

The pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole were not meaningfully altered by saxagliptin. The pharmacokinetics of saxagliptin, BMS-510849, or the exposure to the total active components of saxagliptin (parent + metabolite considering relative differences in potency of DPP4 inhibition) were not meaningfully altered by metformin, glyburide, pioglitazone, digoxin, omeprazole, aluminum hydroxide + magnesium hydroxide + simethicone combination, famotidine, simvastatin, diltiazem, or ketoconazole. Therefore, saxagliptin is not expected to affect the pharmacokinetics of co-administered drugs metabolized by CYP2C8, CYP2C9 or CYP3A4/5, or those that are transported by P-gp or hOCT-1 or -2.

The effects of CYP3A4/5 inducers on the pharmacokinetics of saxagliptin have not been studied. The co-administration of saxagliptin and CYP3A4/5 inducers may result in decreased plasma concentrations of saxagliptin. A drug-drug interaction study of saxagliptin and rifampin, a potent CYP3A4/5 inducer, is currently ongoing.

3.1.2 Special Populations

T2DM, body mass index (BMI), gender, age, race, hepatic impairment, and mild renal insufficiency had no clinically meaningful effects on the pharmacokinetics of saxagliptin or BMS-510849 (Section 2.3 of Module 2.7.2).[9]

Renal excretion was the primary elimination pathway for systemic saxagliptin and BMS-510849 (Section 2.3.2 of Module 2.7.2).[9] Based on renal clearance values, saxagliptin appeared to undergo active renal excretion, whereas BMS-510849 appeared to be only filtered. In subjects with mild renal insufficiency (creatinine clearance 50 - 80 mL/min), AUC values of saxagliptin and BMS-510849 were 16% and 67% higher, respectively, compared with healthy subjects with normal renal function following administration of a single 10 mg dose of saxagliptin. These differences are not considered to be clinically meaningful, and no dosage adjustment is proposed in subjects with mild renal impairment. In subjects with moderate (creatinine clearance 30 to 50 mL/min) and severe renal impairment (creatinine clearance <30 mL/min), AUC values for saxagliptin and/or BMS-510849 were generally greater than 2-fold higher than the AUC values in healthy subjects. Saxagliptin 2.5 mg is the dose recommended in patients with moderate, severe, or end-stage renal disease requiring hemodialysis. This dosing regimen is designed to maintain systemic exposures to saxagliptin and BMS-510849 within the 10 mg QD long-term safety experience, while providing a glycemic-control benefit similar to that attained with 5 mg in subjects with normal renal function.

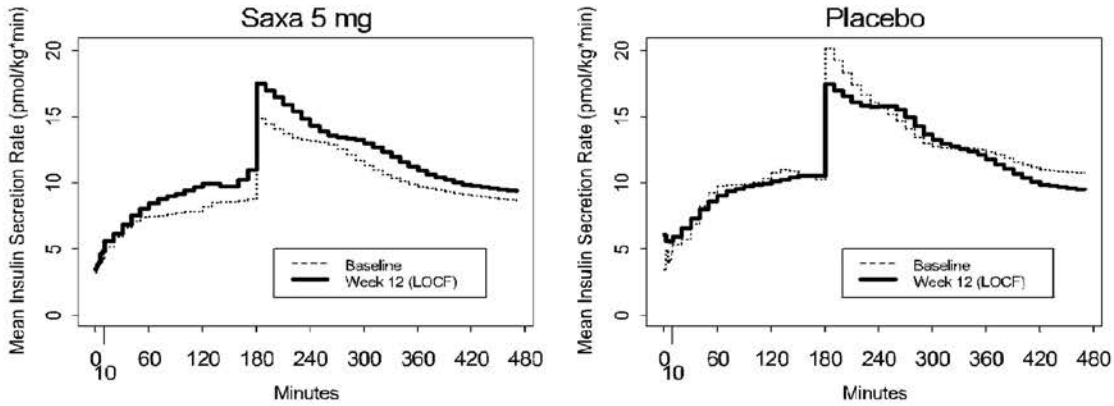
3.2 Pharmacodynamics

In subjects with T2DM, administration of saxagliptin led to inhibition of DPP4 enzyme activity for a 24-hour period (Section 3.5 of Module 2.7.2).[9] After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decrease in glucagon concentrations, and increasing responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin and the decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Over a dosing range of 1 to 400 mg once daily, saxagliptin inhibited DPP4, as measured by plasma DPP4 activity, for at least a 24-hour period. Maximal mean plasma DPP4 inhibition ranged from 86% of pre-dose values with saxagliptin 2.5 mg to 97% after 400 mg of saxagliptin. Maximal plasma DPP4 inhibition did not appear to change substantially upon repeated once daily dosing with any dose of saxagliptin and the extent of inhibition was similar in healthy subjects and subjects with T2DM. DPP4 inhibition at trough was dose-dependent with higher doses providing longer periods of maximum DPP4 inhibition.[32,33,34] The half-life of plasma DPP4 inhibition following a saxagliptin 5 mg dose was 26.9 hours, which supports a once-daily dosing regimen.[35] Saxagliptin consistently decreased both post-prandial and fasting glucose across the Core Phase 3 studies, demonstrating a continued pharmacodynamic effect over the 24 hour period following once-daily dosing. Inhibition of DPP4 activity with long-term dosing of saxagliptin was maintained after 50 weeks of treatment.[36]

Treatment with saxagliptin led to an approximately 2- to 3-fold increase in circulating levels of active GLP-1 and higher C-peptide and insulin concentrations following a mixed meal stimulus.[11] Consistent with this finding, saxagliptin increased pancreatic β-cell responsiveness to glucose in both the fasting and post-prandial state, leading to enhanced insulin secretion and glucose disposal (Figure 3.2).[12] Further, saxagliptin also lowered postprandial glucagon concentrations, thereby counteracting the paradoxical increases in glucagon secretion following meals that are commonly observed in subjects with T2DM. Increases in glucagon secretion stimulate hepatic glucose production and contribute to the glycemic dysregulation observed in subjects with T2DM.[37]

Figure 3.2: **Insulin Secretion Rate During Hyperglycemic Clamp in Conditions of Fasting (0-180 minutes) and Post-OGTT (180-480 minutes) at Baseline and Week 12 (LOCF)**



Data set: Randomized Subjects
Source: Appendix 5.3.4
Program Path: P:/shared/Saxagliptin External Data/CV181041st/val/041st/graphs/final/stepgraphovertime_clamp_bytreat.ssc
Run Date: 24Apr2008 16:05:45 EDT

4 OVERVIEW OF EFFICACY

Data establishing the clinical efficacy of saxagliptin are based on six Core Phase 3 studies: two monotherapy placebo-controlled studies, three add-on placebo-controlled studies (add-on to metformin, SU, and TZD), and one study where saxagliptin was given as initial treatment in combination with metformin.

4.1 Methodology

In all studies, change from baseline to Week 24 in A1C was the primary efficacy endpoint. A1C is a well accepted primary endpoint in clinical trials evaluating compounds for the treatment of hyperglycemia in subjects with T2DM.[7,8] In subjects with T2DM, a number of glycemic endpoints, including A1C, fasting plasma glucose (FPG), and 120-minute postprandial glucose (PPG) concentrations, are directly correlated

with adverse outcomes.[38,39] Data from the Phase 2b and 3 clinical studies show that the saxagliptin 5 mg dose provides clinically meaningful glucose lowering efficacy as reflected in these parameters.

The primary analysis was conducted on the Randomized Subjects data set, defined as all randomized subjects who took at least one dose of double-blind study medication and had a baseline and at least one post-randomization A1C measurement. Missing values were imputed by last observation carried forward (LOCF) methodology. For subjects requiring rescue treatment with an additional oral anti-diabetic agent, the efficacy value obtained most recently before rescue was carried forward in the analysis. Secondary endpoints included change from baseline to Week 24 in FPG and PPG AUC, as well as the proportion of subjects achieving therapeutic glycemic response, defined as A1C < 7% at Week 24 (in accordance with the currently recommended glycemic target from the American Diabetes Association[40]).

For efficacy analyses, data from the studies are presented individually to show consistency of results across studies. In addition, monotherapy data were pooled to assess efficacy and the five placebo-controlled studies were pooled to assess consistency of efficacy in subgroups (Section 1.5.2 of Module 2.7.3).[19]

The long-term efficacy of saxagliptin treatment was assessed by the effect on glycemic parameters (primarily A1C) over time in the Randomized Subjects data set. The long-term effect on glycemic control was also evaluated using two additional data sets: 1) the Completers data set, defined as subjects who completed Week 24 without rescue and 2) the Responders data set, defined as subjects who achieved therapeutic glycemic response of A1C < 7% at Week 24 without being rescued. Efficacy data obtained after the initiation of rescue therapy were excluded from the analyses to avoid confounding the results by the addition of rescue medication.

In the two Phase 3 monotherapy studies (CV181011 and CV181038) and in the initial combination with metformin study (CV181039), subjects were required to be treatment naive upon study entry; subjects receiving chronic antihyperglycemic therapy before enrollment were not eligible. Similarly, in order to enroll in the add-on to metformin (CV181014) study, subjects were required to be on a stable dose of metformin (and no other antihyperglycemic therapies) before study entry; analogous conditions were

required for subject eligibility into the add-on to TZD and SU studies (CV181013 and CV181040 - note that subjects entering CV181040 were switched from their stable, submaximal dose of SU to 7.5 mg open-label glyburide upon entering the lead-in period). These requirements:

1) minimized the need for extended washout and stabilization periods, since the addition or subtraction of medications at study entry were not allowed; and
2) reduced the potential confounding effects associated with changes in treatment regimens instituted at study entry.

The efficacy of saxagliptin was established in a broad range of subjects with T2DM, enabling analyses in representative subpopulations. The range of endpoints in the studies also enabled examination of saxagliptin's mechanism of action, which provided further context and understanding of saxagliptin's glucose lowering effect.

4.2 Results

4.2.1 Short-term Efficacy

In subjects with T2DM, treatment with saxagliptin for 24 weeks consistently provided clinically relevant and statistically significant improvements in A1C. Improvement was seen both in fasting and postprandial glucose, and is compatible with improved β-cell function.

Table 4.2 summarizes results from Phase 2b/3 studies of saxagliptin given as monotherapy or as add-on combination treatment to metformin, TZD or an SU. Statistically significantly larger reductions from baseline in A1C were seen across all studies in the saxagliptin treatment groups compared with control (Table 4.2 and Figures 4.2A, 4.2B, and 4.2C). Treatment with 5 mg saxagliptin led to placebo-subtracted adjusted mean changes in A1C that ranged from -0.40% to -0.83%. The saxagliptin 5 mg groups achieved greater reductions from baseline in A1C than the saxagliptin 2.5 mg groups in five of the six studies. There was no consistent evidence for incremental efficacy benefit at 10 mg beyond that seen for 5 mg.

Table 4.2: A1C, Fasting Plasma Glucose, and Postprandial Plasma Glucose. Difference [95%CI] from Placebo in Adjusted Mean Change from Baseline

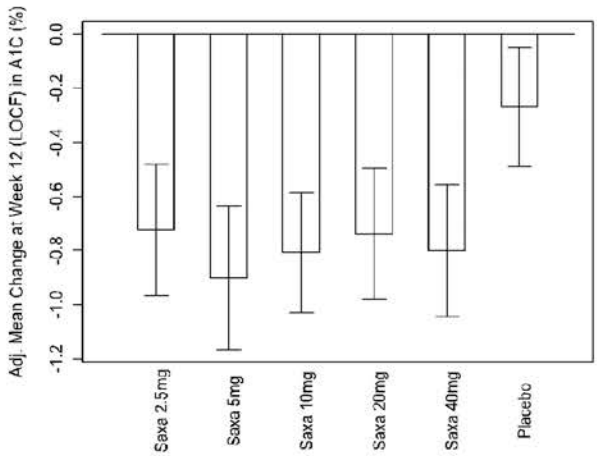
Study	Parameter	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg
CV181008*	A1C**	-0.45 [-0.78, -0.13]	-0.63 [-0.97, -0.29]	-0.54 [-0.85, -0.23]
CV181011		-0.62 [-0.90, -0.33]	-0.64 [-0.93 -0.36]	-0.73 [-1.02, -0.44]
CV181038		-0.45 [-0.74, -0.16]	-0.40 [-0.69, -0.12]	-
CV181013		-0.36 [-0.57, -0.15]	-0.63 [-0.84, -0.42]	-
CV181040		-0.62 [-0.78, -0.45]	-0.72 [-0.88, -0.56]	-
CV181014		-0.73 [-0.92, -0.53]	-0.83 [-1.02, -0.63]	-0.72 [-0.91, -0.52]
CV181008*	FPG**	-13.66 [-25.80, -1.51]	-24.49 [-36.90, -12.07]	-18.72 [-30.21, -7.22]
CV181011		-20.60 [-31.47, -9.72]	-14.73 [-25.50, -3.97]	-22.81 [-33.79, -11.84]
CV181038		-14.7 [-27.2, -2.3]	-14.0 [-26.4, -1.6]	-
CV181013		-11.6 [-19.7, -3.4]	-14.5 [-22.7, -6.3]	-
CV181040		-7.7 [-14.3, -1.1]	-10.3 [-16.9, -3.8]	-
CV181014		-15.55 [-22.55, -8.55]	-23.28 [-30.29, -16.27]	-21.74 [-28.81, -14.68]
CV181008*	PPG AUC**	-1295 [-2129, -462]	-1680[-2587, -772]	-1904 [-2690, -1117]
CV181011		-6221 [-9570, -2872]	-6249 [-9546, -2952]	-7437 [-10798, -4076]
CV181038		-4927 [-8416, -1437]	-5130 [-8630, -1630]	-
CV181013		-5159 [-7333, -2985]	-6579 [-8826, -4333]	-
CV181040		-5492 [-7122, -3862]	-6195 [-7807, -4584]	-
CV181014		-5599 [-7894, -3305]	-6294 [-8606, -3983]	-4845 [-7153, -2537]

*The duration of study CV181008 was 12 weeks, all other studies were of 24 weeks duration. In study CV181008, fasting serum glucose was analyzed (FPG in the other studies), and PPG AUC (0-60 min) was measured after a mixed meal [PPG AUC (0-180 min) was measured after an OGTT in the other studies].

** A1C (%), FPG (mg/dL), PPG AUC (mg*min/dL).

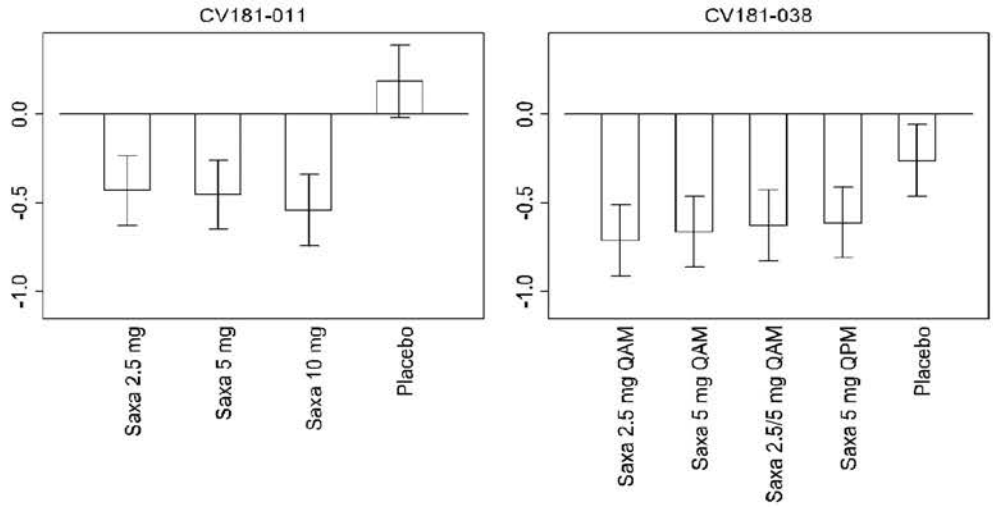
Source: Section 3.2, Module 2.7.3. [19]

Figure 4.2A: **A1C Adjusted Mean Changes from Baseline (95%CI) at Week 12 (LOCF) - Phase 2 Monotherapy Study CV181008**



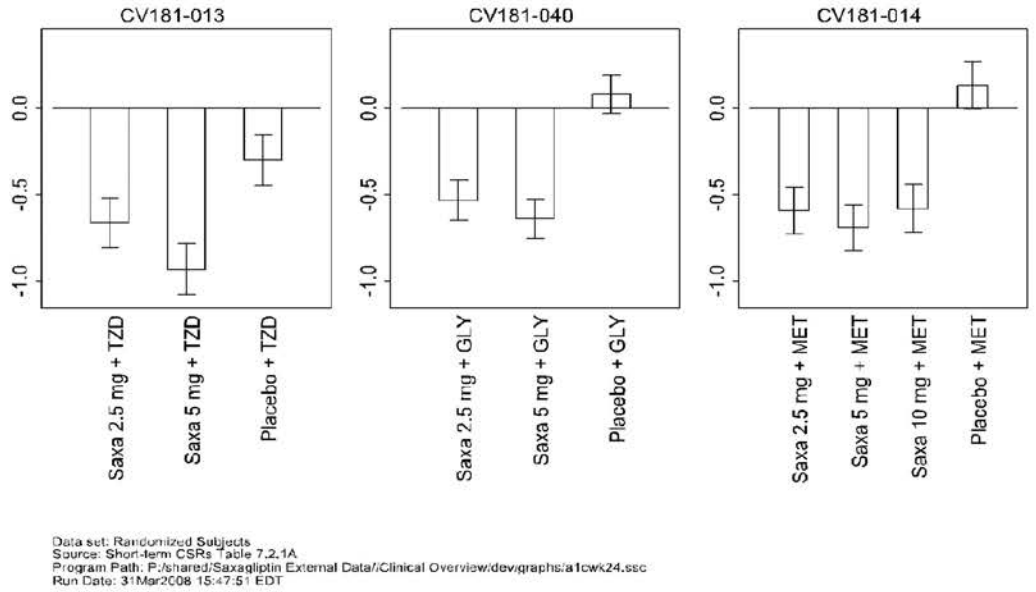
Source: Table 10.1.2A of reference [11]

Figure 4.2B: **A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Monotherapy Studies**



Data set: Randomized Subjects
Source: Short-term CSRs Table 7.2.1A
Program Path: P:/shared/Saxagliptin External Data//Clinical Overview/dev/graphs/a1cwk24.sas
Run Date: 31Mar2008 15:47:51 EDT

Figure 4.2C: A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Add-on Combination Therapy Studies



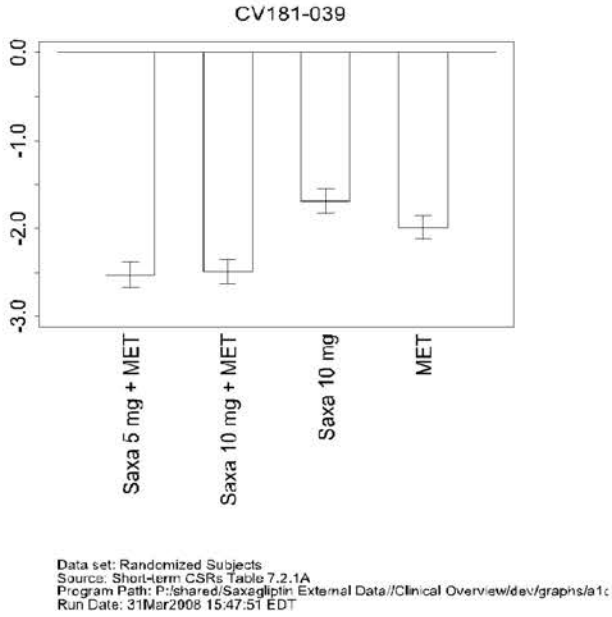
Data set: Randomized Subjects
Source: Short-term CSRs Table 7.2.1A
Program Path: P:/shared/Saxagliptin External Data/Clinical Overview/devgraphs/a1cwk24.sas
Run Date: 31Mar2008 15:47:51 EDT

Similar overall glycemic lowering efficacy was achieved when the saxagliptin 5 mg dose was given in the morning (QAM) and evening (QPM) in study CV181038. The adjusted mean A1C change from baseline to Week 24 in subjects who received saxagliptin 5 mg QAM was -0.66% compared with -0.61% in subjects who received saxagliptin 5 mg QPM.[14]

The reduction in A1C was largest in the initial combination study with metformin (CV181039), which included a treatment naive population with a higher baseline A1C compared with the other studies in the program (Figure 4.2D). The adjusted mean change from baseline in A1C was -2.53% in the saxagliptin 5 mg + metformin group and -2.49% in the saxagliptin 10 mg + metformin group, with larger reductions in subjects with baseline A1C ≥ 9% to < 10% (-2.8%) and ≥ 10% (-3.3%). In the saxagliptin 5 mg + metformin group, the difference (95% CI) in adjusted mean change from baseline was -0.54% (-0.73, -0.35) when compared with metformin monotherapy and -0.84% (-1.03, -0.65) when compared with saxagliptin 10 mg monotherapy. These differences were

statistically significant. Similar decreases in A1C were observed for the saxagliptin 10 mg + metformin group when compared with saxagliptin and metformin monotherapy.

Figure 4.2D: **A1C Adjusted Mean Changes from Baseline (95%CI) at Week 24 (LOCF) - Phase 3 Initial Combination Study CV181039**



Reductions in FPG were observed consistently across all studies (Table 4.2). The impact of treatment with saxagliptin on FPG provided clinical evidence for improvement in basal β-cell function as suggested by increases in HOMA-2β. This improvement may have resulted from amelioration of glucose toxicity or enhanced basal incretin action, or both.[1,41] The proportion of subjects who achieved the pre-specified glycemic goal of A1C < 7% was larger in the saxagliptin treatment groups compared with the control groups (Table 3.2.1.2C and 3.2.2.2B of Module 2.7.3).[19] As was observed for the primary efficacy endpoint, the greatest effect on the endpoints of FPG and the proportion of subjects who achieved A1C < 7% was most frequently seen at the 5 mg saxagliptin dose compared with 2.5 mg, without consistent evidence for incremental efficacy benefit beyond that seen for 5 mg at 10 mg.

There was a decrease from baseline to Week 24 in PPG AUC in the saxagliptin treatment groups compared with placebo (Table 4.2). Similar benefits were observed for the PPG levels measured at 120 minutes after standard oral glucose challenge (Tables 3.2.1.2E, 3.2.2.2D, and 3.2.3.2D of Module 2.7.3).[19] Greater decreases in PPG AUC were seen at the 5 mg saxagliptin dose compared with 2.5 mg in all studies, without consistent evidence for incremental efficacy benefit beyond that seen for 5 mg at the 10 mg dose. The reduction in PPG AUC with higher insulin and C-peptide concentrations during a standard oral glucose challenge provides clinical evidence for the effect of saxagliptin on β-cell function. These findings are consistent with the proposed mechanism of action of saxagliptin, which is thought to enhance incretin action leading to augmentation of glucose-dependent insulin secretion. Improvement in glucose sensing by the α-cells may also have contributed to this observation,[2] as demonstrated by a greater decrease from baseline in postprandial glucagon concentrations at Week 24, an effect reported for other incretin mimetics and DPP4 inhibitors.[42,43]

The placebo-subtracted reduction in A1C was smaller in Study CV181038 than in Study CV181011. While the adjusted mean changes from baseline to Week 24 in A1C observed with the four saxagliptin treatment groups in CV181038 (-0.61% to -0.71%) were larger than those observed in CV181011, the adjusted mean change from baseline in A1C of -0.26% in the placebo group in CV181038 was larger than observed in CV181011. The protocols specified that subjects were to receive exercise and dietary instruction as per local guidelines throughout the study. The reduction in A1C as well as the moderate reduction in weight observed in the placebo group (1.3 kg) in CV181038 supports the notion that the dietary and exercise intervention were followed by subjects in this group. Adherence to diet and exercise intervention in the context of a low A1C and FPG at baseline may have also lessened the additional A1C reduction induced by saxagliptin, particularly given the glucose-dependent mechanism of action of DPP4 inhibitors. The mean FPG at baseline was lower in CV181038 (162 mg/dL) than in CV181011 (175 mg/dL).

Based on evaluations of A1C reduction in multiple subgroup populations, treatment with saxagliptin consistently demonstrated a beneficial antihyperglycemic effect across subgroups of demographic and baseline diabetes characteristics (eg, age, gender, race, see Section 3.3 of Module 2.7.3).[19] Saxagliptin produced greater reductions in A1C from

baseline for subgroups with higher baseline A1C, typical of drugs used for the treatment of diabetes.

There were clinically meaningful reductions in A1C for monotherapy and combination therapy groups regardless of age, comparing subjects < 65 and ≥ 65 years. While the number of subjects ≥ 75 years was low (1.4% of subjects in the Core Phase 3 studies, see Appendix 3.5 of the Integrated Summary of Efficacy), the A1C reductions were comparable to the younger age groups (Appendix 5.11.5 and 5.11.6 of the Integrated Summary of Efficacy).

No clinically meaningful changes in fasting lipid parameters were observed following treatment with saxagliptin.

4.2.2 Long-term Efficacy

Interim analyses were performed on the efficacy results from ongoing long-term extensions of the six Core Phase 3 studies. Results obtained after the initiation of rescue treatment were not included in any efficacy analyses. The studies with the longest duration of follow-up at the time of data cutoff (monotherapy study CV181011 and the add-on-to metformin study CV181014) include efficacy data up to 102 weeks of treatment.

In all studies, treatment with saxagliptin was associated with a greater reduction in A1C than control, and the effect was sustained up to 102 weeks (assessed in Studies CV181011 and CV181014, see Section 5 of Module 2.7.3).[19] The control-group subtracted adjusted mean change from baseline in A1C at Week 102 in the saxagliptin 5 mg treatment groups was -0.45% in Study CV181011 and -0.72% in Study CV181014. Although the shape of the A1C concentration curves varied by study, a difference relative to control persisted in all studies. Continued separation between saxagliptin and control with respect to A1C lowering was observed in both Phase 3 monotherapy studies, even though all subjects in the control groups who completed Week 24 without rescue had blinded metformin 500 mg added to their treatment regimen.

There are limitations in the analyses of the long-term interim data. Interpretation of efficacy parameters was complicated by glycemic rescue criteria, which became stricter

in the long-term treatment period, leading to an increased number of subjects being rescued or discontinued. In general, a greater proportion of subjects in the control groups compared with the saxagliptin treatment groups discontinued from the studies or received rescue treatment throughout the short-term and long-term treatment periods due to the glycemic rescue criteria. Because the studies are still ongoing, visits for some subjects are pending. This limitation will be mitigated in the final analyses when the studies are completed.

4.2.3 Relevance and Applicability of Efficacy Data for Dosing

The efficacy results from the 8 clinical studies in the saxagliptin Phase 2b and 3 program in over 4600 subjects support the oral dose of saxagliptin 5 mg once daily in a wide range of subjects with T2DM, in either monotherapy, add-on combination therapy with metformin, a TZD, a SU, or initial combination therapy with metformin.

Based on consistency and magnitude of glycemic effect, saxagliptin 5 mg is the optimal dose. There was no evidence that the 10 mg saxagliptin dose offered any incremental glycemic benefits to those observed with the 5 mg dose. Subjects in the saxagliptin 5 mg groups consistently achieved better glycemic control than the subjects who received saxagliptin 2.5 mg. In all studies except for CV181038 (where the adjusted mean change from baseline to Week 24 in A1C was -0.66% for the saxagliptin 5 mg group and -0.71% for the 2.5 mg group), the saxagliptin 5 mg group consistently demonstrated greater decreases from baseline in A1C than the saxagliptin 2.5 mg group; the magnitude of difference in A1C change from baseline favoring the 5 mg over the 2.5 mg dose ranged from 0.02% to 0.26%. The proportion of subjects who achieved A1C reductions $\geq$ 0.7% was similarly greater in subjects who received saxagliptin 5 mg compared with 2.5 mg in all studies except CV181038. In addition, there was a greater reduction from baseline in PPG AUC for the saxagliptin 5 mg groups compared with the 2.5 mg groups in all Phase 3 studies and the dose-ranging Phase 2b study CV181008. PPG AUC, a measure of the primary mechanism of action for saxagliptin, aligns with the primary endpoint of A1C lowering, and supports the recommendation that saxagliptin 5 mg per day is the optimal dose.

5 OVERVIEW OF SAFETY

5.1 Safety Background

Saxagliptin belongs to the DPP4 inhibitor class of compounds. DPP4 is a widely expressed cell surface peptidase that has been shown to cleave a large number of chemokines and peptides in vitro; however, relatively fewer physiologic substrates for DPP4 have been identified in vivo.[44] Cell surface DPP4, also known as CD26, has been reported to function as a co-stimulatory signaling molecule in T-lymphocyte activation. It is not known if DPP4 enzymatic activity per se is integral to the possible function of DPP4/CD26 as an immune co-stimulatory signaling molecule. Safety and tolerability considerations that have been raised in association with members of the DPP4 inhibitor class include the occurrence of skin-related lesions [observed in nonclinical (monkey) toxicology studies], gastrointestinal toxicity (observed in dogs)[45], hypersensitivity reactions,[46] localized edema of the hands and feet[22], abnormalities in liver function test[47], increased reports of infections[48], and increases in serum creatinine.[49]

5.1.1 Nonclinical Safety

Results of the nonclinical pharmacology and safety testing of saxagliptin were predictive of a low potential for clinically significant adverse events in clinical trials.[50]

The toxicity of saxagliptin was evaluated in mice, rats, dogs, and monkeys at exposures which were comparable to or markedly higher than the human therapeutic exposure in a comprehensive battery of GLP-compliant nonclinical toxicology studies. In rats, the major target organ changes were generally minimal splenic lymphoid hyperplasia, pulmonary histiocytosis, and mononuclear-cell infiltrates/inflammation in the ocular accessory gland and liver in short and long-term studies, and after 104 weeks of dosing, the lung, urinary bladder, and epididymis. These findings reflected exaggerated pharmacologic effects and are of little toxicologic significance because they were limited in severity (never beyond mild), were non-progressive, and occurred only at clinically non-relevant exposures (AUC multiples ≥ 36x). In dogs, the major finding was gastrointestinal (GI) toxicity characterized by bloody/mucoid feces (AUC multiple of

19x) and enteropathy (AUC multiple of 580x).[51] Clinical correlates to the bloody/mucoid feces observed in dogs have not been associated with saxagliptin in human clinical trials.

In monkeys, major target organ changes included reversible erosive and/or ulcerative skin lesions with scab formation and reversible multi-tissue mononuclear-cell infiltrates. The AUC at the NOEL for these changes was 1 to 3x the recommended human dose of 5 mg and demonstrated that DPP inhibition is observed in the absence of toxicity. The underlying mechanism(s) for these changes is currently unknown, but to date there has been no clinical evidence of similar skin lesions in humans treated for up to 2 years with saxagliptin (see Section 5.2.4.2).

Saxagliptin was not genotoxic based on the weight of evidence from a battery of genotoxicity studies and was not carcinogenic in rodents at large exposure multiples relative to the 5 mg human dose (up to 1210x in mice and 370x [males] to 2300x [females] in rats). Saxagliptin was not teratogenic at any dose in rats or rabbits. With the exception of delayed ossification in the rat (maternal AUC multiple of 560x), all reproductive and developmental toxicities were observed at maternally toxic doses.

To date, inhibition of cell surface DPP4/CD26 peptidase catalytic activity on T lymphocytes has not been physiologically coupled to lymphocyte activation. However, the role of the catalytic activity of DPP4 on T-lymphocyte biology has yet to be fully defined. To address the potential relationship of saxagliptin DPP4 inhibitory activity to T lymphocyte activation, a series of studies was conducted to assess T-lymphocyte activation and cell surface DPP enzyme activity in the presence or absence of saxagliptin. In freshly isolated human T lymphocytes, inhibition of T-lymphocyte activity only occurred at concentrations much higher than that required to inhibit cell-surface DPP4 catalytic activity. Similarly, following oral dosing in rats at high saxagliptin exposures (~335x), T lymphocyte-mediated immune function was not altered, suggesting that therapeutic levels of saxagliptin are unlikely to interfere with CD26-dependent T-cell activation.

5.1.2 Safety Monitoring in Phase 3 Studies

At the start of the Phase 3 clinical development program, an independent Data Monitoring Committee (DMC) was established. The DMC periodically reviewed the

accumulating safety data on saxagliptin, including findings from the six large Core Phase 3 studies. The DMC has allowed all studies in the saxagliptin Phase 3 program under its review to continue without modification at all doses under evaluation.

To complement standard safety monitoring practices, an extensive program to monitor and collect information on events of special interest was implemented. Events were identified as being of special interest based on findings observed in the saxagliptin non-clinical and Phase 1 and 2b programs, safety-related concerns reported for other DPP4 inhibitors, and theoretical considerations related to the mechanism of action of DPP4 inhibitors. The events of interest included: (1) events related to skin lesions; (2) selected infections (eg, events related to herpes simplex virus or Mycobacterium tuberculosis); (3) decreased lymphocyte counts; (4) decreased platelet counts; and (5) events of localized edema. Plans to monitor these events were reviewed and approved by US FDA.[23,24] In consultation for scientific advice with the CHMP, the safety monitoring and handling plan was considered appropriate and adequate. Monitoring activities included ongoing identification of cases and deployment of supplemental case report forms to gather additional information on AEs of skin lesions, decreased lymphocyte counts, decreased platelet counts, selected infections, and symptomatic edema of the hands and feet. Algorithms were developed to guide investigators in managing subjects who demonstrated decreases in lymphocyte and platelet counts as well as findings related to liver function test abnormalities and CK elevation. Special case report forms were also used throughout the Phase 3 program to gather details for all reported events of hypoglycemia.

Based on review of data from the Phase 3 program, the DMC endorsed a change to remove exclusions to study entry based on low platelet and lymphocyte counts, leading to an amendment of the CV181039 protocol (amendment 6).[18] In accordance with this change, there are no exclusion criteria that specifically relate to low platelet and lymphocyte counts in the recently initiated Phase 3b studies.

Investigators received instruction regarding the use and implementation of the special case report forms. As a result, this instruction likely heightened awareness of these events by the Investigators, which could have resulted in a higher frequency of reported events and a tendency of assigning a positive relationship to study treatment.

5.2 Safety Results

Saxagliptin was safe and well tolerated in all clinical trials at doses of up to 400 mg QD for 2 weeks, 100 mg QD for 6 weeks, 40 mg QD for 12 weeks, and at 2.5, 5, and 10 mg QD for up to 102 weeks (see Module 2.7.4).[10] Saxagliptin, at a daily dose of 5 mg, resulted in a clinical adverse event profile that was similar to placebo. The majority of reported adverse events were of mild intensity and did not require treatment discontinuation. The safety profile was generally consistent when saxagliptin was given as monotherapy, as add-on combination treatment to metformin, SU, or TZD, and as initial therapy in combination with metformin.

5.2.1 Exposure

A total of 5346 subjects were studied in the saxagliptin Phase 1-3 clinical program, of which 4042 subjects received saxagliptin (see Figure 1.1 and Section 1.2 of Module 2.7.4).[10] In the Phase 2b/3 program, which included eight studies in total, 3422 subjects received saxagliptin, including 66 subjects who received open-label saxagliptin 10 mg in Study CV181011, and 1251 received placebo or control treatment. Overall, 937, 1269, and 1066 subjects received saxagliptin at doses of 2.5 mg, 5 mg, and 10 mg, once daily. There is substantial exposure beyond the 24-week short-term treatment period. The total number of subjects exposed to saxagliptin (2.5 mg, 5 mg, or 10 mg) for > 48 weeks included 303 subjects in monotherapy studies, 451 subjects in the add-on combination study with metformin, 369 subjects in the add-on combination study with SU, 195 subjects in the add-on combination study with TZD, and 141 subjects in the initial combination therapy with metformin. Unless otherwise specified, the safety findings described below are based on exposure up to 24 weeks in duration.

5.2.2 Adverse Events

In studies of saxagliptin as both monotherapy and in combination with other oral antihyperglycemic agents, the clinical AE profile of saxagliptin 5 mg was generally similar to placebo (Section 2.1 of Module 2.7.4).[10] The overall incidence of adverse events (including AEs of hypoglycemia) in subjects treated with saxagliptin 5 mg was similar to placebo (72.2% compared with 70.6%), based on a pooled analysis of five

Phase 3, placebo-controlled studies that included two monotherapy studies (CV181011 and CV181038), the add-on to metformin study (CV181014), the add-on to TZD study (CV181013), and the add-on to glyburide study (CV181040). Furthermore, there was no discernible difference in the clinical AE profile between the saxagliptin 2.5 mg and 5 mg doses.

In the placebo-controlled Pooled Monotherapy Population, the frequency of reported AEs (including hypoglycemia) was higher in subjects who received any of the 3 doses (2.5, 5, or 10 mg) of saxagliptin compared with placebo (67.8% compared with 60.9%). This difference was, in part, a reflection of a higher frequency of reported AEs in the saxagliptin 10 mg group (77.6%) compared with the saxagliptin 2.5 mg and 5 mg groups (66.0% and 65.9%, respectively). In contrast, in an active-comparator monotherapy experience within the initial combination with metformin study (CV181039), the frequency of all reported AEs for subjects treated with saxagliptin monotherapy at 10 mg was lower than that for subjects receiving metformin monotherapy (53.4% and 58.5%, respectively).

In the add-on combination studies, saxagliptin 5 mg was associated with a slightly higher frequency of AEs (including hypoglycemia) in combination with metformin (70.2% compared with 64.8%) and in combination with TZD (74.2% compared with 66.8%), and a slightly lower frequency of AEs in combination with SU (72.3% compared with 76.8%). The frequency of AEs in the initial combination study with metformin was comparable or lower in each of the saxagliptin groups relative to metformin monotherapy (55.3%, 57.3%, 53.4%, and 58.5% for the saxagliptin 5 and 10 mg + metformin combinations, saxagliptin 10 mg, and metformin, respectively).

The sponsor examined AEs that occurred in ≥ 2% of subjects in the individual studies as well as in the pooled data sets. To identify specific adverse reactions associated with saxagliptin and to provide information regarding the safety of saxagliptin considered most useful to healthcare practitioners making treatment decisions, two complementary approaches to evaluate the safety database were undertaken. These included analyses of AEs in individual populations (ie, by treatment indication) followed by analyses of pooled data from the five Phase 3 placebo-controlled studies. Pooling of safety data from multiple studies:

1) increases the precision of AE rates;
2) reduces the likelihood for chance safety findings that are not associated with the drug; and
3) allows for discernment of less frequently reported AEs that can then be appropriately included in labeling.

Alternatively, evaluating safety data in individual populations enables the identification of adverse reactions unique to populations receiving specific concomitant antihyperglycemic agents. Together, these complementary approaches enhanced the ability to understand the safety profile of saxagliptin and describe adverse drug reactions.

The five placebo-controlled studies were pooled apart from the active-controlled, initial combination with metformin study (CV181039), given the design differences between the studies (active-controlled compared with placebo-controlled and the presence of two control groups within CV181039). The safety database of the initial combination study with metformin was large, included 1,306 subjects, and was able to serve as its own independent dataset.

For the presentation of common adverse reaction data, a ≥ 5% threshold was selected based upon a review of several labels of approved drugs for the management of diabetes. The overall approach was to present data based on analyses of the five-study, pooled placebo-controlled data set. This allowed for a unified presentation of common (≥ 5%) and less common adverse reactions (≥ 2% with some basis to believe there is a causal relationship between the drug and the event - here, defined as a ≥ 1% higher frequency in the saxagliptin 5 mg group compared with placebo) generally associated with saxagliptin treatment with increased precision and lack of redundancy. Findings were supplemented by analyses of the individual populations by treatment indication to ensure population-specific adverse reactions were appropriately identified.

The specific adverse reactions generally associated with the use of saxagliptin 5 mg as compared with placebo in the placebo-controlled studies were:

- Adverse reactions (≥ 5%): upper respiratory infection (7.7% and 7.6%), urinary tract infection (6.8% and 6.1%), and headache (6.5% and 5.9%)

- Adverse reactions (≥ 2% and ≥ 1% higher frequency in the saxagliptin 5 mg group compared with placebo): sinusitis (2.6% and 1.6%), gastroenteritis (2.3% and 0.9%), and vomiting (2.3% and 1.3%).

Specific adverse reactions associated with the use of saxagliptin 5 mg as compared with placebo in individual populations receiving specific concomitant antihyperglycemic agents were:

- In the add-on combination study with TZD: peripheral edema (8.1% and 4.3%)
- In the add-on combination study with SU: hypoglycemia (14.6% and 10.1%)

In the initial combination study with metformin, the specific adverse reactions associated with the use of saxagliptin 5 mg as compared with saxagliptin monotherapy or metformin monotherapy were:

- Common (≥ 5%) adverse reactions: headache (7.5%, 6.3%, and 5.2%), and nasopharyngitis (6.9%, 4.2%, and 4.0%)

Analyses of the long-term extensions of the Core Phase 3 studies, which included data up to 102 weeks in duration, did not reveal any unexpected events or emergent safety signals when compared with analyses of the respective short-term (24-week) study periods. The overall clinical AE profile based on exposure up to 2 years was consistent with that observed at 24 weeks.

When given as monotherapy, saxagliptin 5 mg was weight neutral in CV181011. Treatment with saxagliptin 5 mg led to small decreases in weight in CV181038 compared with a small, but greater numerical reduction in weight observed in subjects in the placebo group. In the add-on to metformin study, similar decreases in weight were observed in subjects who received saxagliptin 5 mg and placebo. In the add-on to SU and TZD studies, small increases in weight were seen in subjects given saxagliptin, which were numerically higher but of generally comparable magnitude to those seen in the control group. Saxagliptin treatment did not lead to any adverse effects in lipid parameters or vital signs.

Saxagliptin was not associated with clinically significant prolongation of QTc interval at daily doses up to 40 mg. Likewise, there was no apparent effect of saxagliptin 10 or 40 mg on heart rate. Saxagliptin and BMS-510849 plasma concentrations were not correlated with QTc interval following administration of 10 or 40 mg saxagliptin to healthy subjects.

5.2.3 Deaths, Serious Adverse Events, and Adverse Events Leading to Discontinuation

The frequency of deaths in the Phase 2b/3 studies was similar in subjects who received saxagliptin and placebo (Section 2.1.2 of Module 2.7.4).[10] In the Phase 2b and 3 studies, a total of 16 deaths were reported; 2 subjects (0.2%) each in the saxagliptin 2.5 and 5 mg groups, 3 subjects (0.3%) in the saxagliptin 10 mg group, 5 subjects (0.5%) treated with placebo, and 4 subjects (1.2%) treated with metformin. There was 1 death in a subject with a history of hepatic impairment who received saxagliptin in clinical pharmacology study CV181020.

The frequency of SAEs was generally comparable between the saxagliptin and control groups throughout the six Core Phase 3 studies (ie, saxagliptin given as monotherapy, as add-on combination treatment to metformin, TZD and SU, or as initial combination therapy with metformin; Section 2.1.3 of Module 2.7.4).[10] In the five pooled placebo-controlled monotherapy and combination studies, the proportion of subjects with SAEs was 3.4% in subjects who received saxagliptin 5 mg and 3.4% in subjects who received placebo. Serious adverse events (SAEs) were uncommon in all studies, and there was no predominance of any single, specific SAE associated with saxagliptin treatment. In the individual studies, SAEs considered to be related to study drug (≤ 0.9%) or leading to discontinuation (≤ 1.6%) were infrequent in subjects who received saxagliptin and occurred at rates generally comparable to that of placebo.

The frequency of AEs leading to discontinuation from study therapy was generally low in all treatment groups (Section 2.1.4 of Module 2.7.4).[10] In the placebo controlled studies, AEs leading to discontinuation were reported in 2.2%, 3.3%, 3.9%, and 1.8% of subjects in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. The most frequent AEs (>1 subject, based on preferred term) leading to study discontinuation,

which were numerically higher in subjects who received saxagliptin compared with placebo were: lymphopenia, blood CK increased, blood creatinine increased, nausea, and eye pain. Rates of discontinuation for rash were similar in subjects who received saxagliptin and placebo, whereas the rate of discontinuation for AEs of weight increased, depression, and angina pectoris were higher in subjects who received placebo compared with saxagliptin. In the initial combination therapy study with metformin, AEs leading to discontinuation were numerically lower in each of the treatment groups which contained saxagliptin compared with metformin monotherapy (2.5%, 2.2%, 2.4%, and 3.4% for the saxagliptin 5 and 10 mg + metformin combinations, saxagliptin 10 mg, and metformin, respectively). The most common AEs leading to discontinuation from study in the metformin monotherapy group were from the SOC Gastrointestinal Disorders.

5.2.4 Additional Safety Considerations

5.2.4.1 Hypoglycemia

In subjects who received saxagliptin 5 mg as monotherapy or in combination with metformin or TZD, the frequency of reported hypoglycemia was low, with rates similar to those reported in subjects who received placebo (Section 2.3.1 of Module 2.7.4).[10] In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to TZD study, the overall incidence of reported hypoglycemia in subjects treated with saxagliptin 5 mg (4.8%) was similar to placebo (4.3%). The incidence of reported hypoglycemia in the saxagliptin 10 mg monotherapy group was 1.5% compared with 4.0% in the metformin monotherapy group in Study CV181039. Events of confirmed hypoglycemia (defined as symptoms of hypoglycemia and with fingerstick blood glucose measurement $\leq$ 50 mg/dL) were infrequent and occurred at similar rates for saxagliptin 5 mg and placebo. Medical assistance was not required for any of the confirmed events of hypoglycemia.

While the incidence of hypoglycemia was numerically higher for subjects who received saxagliptin 5 mg compared with control when added to an intermediate dose of SU in study CV181040, the difference (14.6% compared with 10.1%) was not statistically significant. The rate of confirmed hypoglycemia was 0.8% in the saxagliptin 5 mg treatment group and 0.7% in the control group in Study CV181040.

5.2.4.2 Skin-related Adverse Events

The frequency of skin-related adverse events was generally comparable between subjects who received saxagliptin 5 mg and placebo (Section 2.3.2 of Module 2.7.4).[10] In an analysis of the five pooled placebo-controlled monotherapy and combination studies, the proportion of subjects with AEs in the SOC Skin and Subcutaneous Tissue Disorders was 7.1% in subjects who received saxagliptin 5 mg, and 7.3% in subjects who received placebo. In the individual studies, there was no consistent evidence for a dose-response relationship for AEs in this SOC.

In non-clinical toxicology studies where saxagliptin was administered to cynomolgus monkeys, reversible erosive and/or ulcerative skin lesions with scab formation were observed. In order to identify events in Phase 3 studies that were potentially reflective of the non-clinical dermatologic findings in monkeys, a predefined MedDRA preferred term list was developed. The list, which included preferred terms such as skin ulcer and skin necrosis, was used to identify adverse events in the Phase 3 clinical database for further evaluation. Adverse events, as specified in the pre-defined list of preferred terms, were reported infrequently, without clear imbalance between the saxagliptin and control groups. No events were observed with saxagliptin 10 mg in the Core Phase 3 studies. In general, the causes of the identified skin lesions from this list were believed to be secondary to underlying disease (eg, diabetic ulcers) or related to trauma.

Overall, evaluation of clinical data has not revealed any signals that correlate to the skin findings in the cynomolgus monkey; therefore, there is no evidence that the findings in the monkey are applicable to humans.

5.2.4.3 Infection-related Adverse Events

Infection-related AEs were identified as an event of special interest given the role of DPP4, also known as CD26, as a co-stimulatory signaling molecule expressed on the surface of T-cells. An analysis of the five pooled placebo-controlled monotherapy and combination studies demonstrated comparable AE frequencies in the SOC Infections and Infestations in the saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo groups (36.4%, 35.9%, and 34.8%, respectively); a higher frequency of AEs was observed in the saxagliptin 10 mg group (40.1%) (Section 2.3.3 of Module 2.7.4).[10] As preferred terms,

sinusitis and gastroenteritis were AEs with some basis for an association with the use of saxagliptin in an integrated safety analysis across the core Phase 3 studies.

In treatment-naive subjects, saxagliptin given as monotherapy was associated with a higher reported frequency of infection-related AEs compared with placebo (31.5% and 23.7%). In contrast, the frequency of AEs reported in this SOC for treatment-naive subjects who received saxagliptin monotherapy at 10 mg in CV181039 was similar to the frequency in those who received metformin monotherapy (26.6% and 23.5%, respectively). In the add-on combination studies, saxagliptin was associated with a comparable frequency of infection-related AEs in combination with SU and a marginally higher frequency in combination with either metformin or TZD.

Although AEs in the SOC Infections and Infestations were the most commonly reported AEs across the Core Phase 3 studies, relatively few were considered serious, and few led to discontinuation. The frequency of events reported as SAEs or as leading to discontinuation of study drug in this SOC was similar in subjects who received saxagliptin and placebo (approximately 0.5%). Infection-related events that would be considered as opportunistic infections were infrequent, with no indication of an increased rate in subjects who received saxagliptin in the Core Phase 3 program.

5.2.4.4 Localized Edema Adverse Events

Localized edema was considered an event of special interest given reports of symptomatic edema of the hands and feet in subjects who received another member of the DPP4-inhibitor class.[22] Adverse events of localized edema in the saxagliptin Phase 3 program were identified using a pre-defined list of lower-level terms.

Across the saxagliptin Phase 3 program, the incidence of localized edema was generally comparable between saxagliptin- and placebo-treated subjects (Section 2.3.6 of Module 2.7.4).[10] The sole deviation from this generalization occurred in the saxagliptin 5 mg group of the add-on combination study with TZD (CV181013). In this study, there was a higher rate of events constituting localized edema in the 5 mg saxagliptin group compared with placebo, whereas the rate was lower in the saxagliptin 2.5 mg group compared with placebo. The majority of these events in the saxagliptin 5 mg plus TZD group were for pedal edema; there was no imbalance seen for events of hand edema. It is

well established that peripheral edema is associated with TZD therapy, and that this finding is more common when a TZD is used concomitantly with other oral diabetes agents.[52] Across the clinical program, the majority of localized edema AEs were of mild to moderate intensity and did not result in discontinuation of study drug. In a clinical pharmacology study, saxagliptin was well tolerated at doses of up to 400 mg given for 14 days without any reports of localized edema of the hands or feet. Overall, there was no evidence that saxagliptin led to an increased risk of localized edema as reported in subjects who received another member of the DPP4 inhibitor class.

5.2.4.5 Cardiovascular Adverse Events

A pre-defined list of preferred terms was developed during the Phase 3 program to identify cardiovascular (CV) AEs which were indicative of acute cardiac and cerebrovascular events. In an analysis of the five pooled placebo-controlled monotherapy and combination studies, the proportion of subjects with CV AEs was similar in subjects who received saxagliptin 5 mg (0.2%) and subjects who received placebo (1.0%) (Section 2.3.7 of Module 2.7.4).[10] The rate for all subjects who received saxagliptin, including doses of 2.5, 5, and 10 mg was 0.3%. There was no evidence for a dose-response relationship with CV events for saxagliptin doses of 2.5 through 10 mg. CV events were infrequent in each of the individual studies.

5.2.4.6 Hypersensitivity Reaction Adverse Events

Potential AEs related to hypersensitivity reactions were identified in the short- and long-term periods of the Core Phase 3 studies by matching reported AEs to an extensive predefined list of PTs. Overall, relatively few "hypersensitivity" AEs were reported in the Phase 3 clinical development program (Section 2.3.9 of Module 2.7.4).[10] In the five placebo-controlled studies, the frequency of hypersensitivity AEs based on the pre-defined list ranged from approximately 0.4% to 3.2% in subjects who received saxagliptin 5 mg compared with a range of 0% to 1.8% in subjects who received placebo. The rates of hypersensitivity reactions were comparable in all treatment groups in the initial combination study with metformin (CV181039). The vast majority of all adverse events that fell into this category were reported as mild to moderate in intensity and did not result in study drug discontinuation.

Two subjects in the Phase 2b/3 studies reported an AE with the preferred term angioedema. One AE was reported in a subject who received saxagliptin 5 mg and 1 in a subject who received placebo. The saxagliptin-treated subject had a past medical history significant for chronic idiopathic urticaria and angioneurotic edema. The AE was considered not likely related to study drug by the investigator and the subject continued in the study. The AE in the subject in the placebo group was reported "angio edema worsening", and led to interruption of study drug.

5.2.5 Safety in Special Populations

In general, the clinical adverse event profile of saxagliptin did not differ consistently within major subgroups, including by gender, age (< 65 and ≥ 65 years), race, ethnicity, BMI, duration of diabetes, and degree of renal insufficiency (Section 5 of Module 2.7.4).[10]

5.2.6 Laboratory Findings

5.2.6.1 Lymphopenia

Overall, a small decrease in mean absolute lymphocyte count was observed at a dose of saxagliptin 5 mg (Section 3.1 of Module 2.7.4).[10] The mean decrease was approximately 100 cells/μL relative to placebo (from a baseline absolute lymphocyte count of approximately 2200 cells/μL) based on a pooled analysis of five placebo-controlled clinical studies. Mean lymphocyte counts remained stable and within normal limits with daily dosing up to 102 weeks in duration. The frequency of investigator reported AEs for lymphopenia was similar for subjects who received saxagliptin and placebo (Section 2.3.4 of Module 2.7.4).[10] While the clinical significance of the decreases in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant adverse events.

In two clinical pharmacology drug-drug interaction studies [CV181005 (ketoconazole) and CV181017 (metformin)], a flu-like syndrome was observed in subjects who received a second dose of saxagliptin 100 mg separated from the first dose by 7 to 14 days.[53,54] Where measured, all subjects who experienced the flu-like syndrome had absolute

lymphocyte counts below the lower limit of normal; however lymphocyte counts had returned to baseline values within 72 hours of the second 100 mg dose of saxagliptin. The flu-like syndrome and transient decrease in lymphocyte counts have not been associated with daily saxagliptin doses of up to 400 mg QD for 2 weeks, 100 mg QD for 6 weeks, 40 mg QD for 12 weeks, and 2.5, 5, and 10 mg QD for up to 2 years, nor with interrupted dosing of saxagliptin up to 40 mg.

In a study designed to further understand the mechanism underlying the decrease in lymphocyte count, saxagliptin was given at a dose of 40 mg.[55] In a subset of subjects who were rechallenged with 40 mg saxagliptin after a 1 week interruption following 2 weeks of QD dosing, larger decreases in absolute lymphocyte counts were seen. Lymphocyte immunophenotyping did not suggest that any one lymphocyte population was disproportionately affected when decreases were observed. Total lymphocytes were stained with markers to distinguish apoptosis and necrosis; no detectable increase in apoptosis or necrosis was observed in any groups at any time throughout the study. In addition, no clear decrease of T-cell proliferation was detected after saxagliptin dosing. Thus, while the mechanism for the decreases in lymphocyte count remains unknown, the mechanism did not appear related to a defect in lymphocyte proliferation or increased destruction of lymphocytes.

In the dose-ranging Phase 2b study (CV181008), a reversible, dose-related decrease in mean lymphocyte count was observed during dosing with saxagliptin. Decreases compared with placebo were most apparent at doses of saxagliptin greater than 10 mg once daily (ie, 20, 40, and 100 mg QD) and were of the magnitude of 200-400 cells/μL, from a baseline mean lymphocyte count of approximately 1.8-2.0 x 10^3 cells/μL. Mean absolute lymphocyte count was stable and remained within normal limits throughout the double-blind treatment period in all treatment groups. In addition, mean lymphocyte count returned to baseline during the 4 week recovery period after end of dosing.

As a consequence of these findings, lymphocyte counts were monitored frequently in the Phase 3 program. Pre-defined lists of AEs were developed to identify and gather additional information on these events in an ongoing manner. Treatment algorithms, including protocol mandated criteria for discontinuation and study drug interruption

based on lymphocyte count, were implemented to guide investigators in cases where decreased lymphocytes were noted.

In the Phase 3 program, treatment with saxagliptin 10 mg was associated with a small but measurable reduction in lymphocyte count based on assessments of mean lymphocyte count over time and the proportion of subjects reaching predefined reductions of $\geq 10\%$, $\geq 20\%$, and $\geq 30\%$ from baseline. Conversely, saxagliptin 2.5 mg did not demonstrate any consistent or meaningful declines in lymphocyte count compared with placebo by these measures. The 5 mg dose was associated with a small, but measurable decline in lymphocyte count relative to placebo that was smaller in magnitude relative to that observed with saxagliptin 10 mg. From a baseline absolute lymphocyte count of approximately 2200 cells/μL, a mean decrease of approximately 100 cells/μL relative to placebo was observed in subjects who received saxagliptin 5 mg in a pooled analysis of five placebo-controlled clinical studies. In the 10 mg saxagliptin group, the observed reduction was approximately 120 cells/μL relative to placebo. Mean lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. Analyses of terciles by baseline absolute lymphocyte count did not identify a reduction of the lymphocyte count for the saxagliptin 2.5 and 5 mg treatment groups in the tercile with the lowest absolute lymphocyte count at baseline.

A dose-related pattern of effect was also observed when evaluating marked abnormalities of lymphopenia, defined as a lymphocyte count ≤ 750 cells/μL. In the subjects with non-isolated declines in absolute lymphocyte count, most were re-challenged without recurrence. The frequency of lymphopenia adverse events reported by investigators was similar for subjects who received saxagliptin versus placebo in the placebo-controlled Phase 3 studies (1.0% for all subjects who received saxagliptin versus 1.0% for placebo). None of the events of lymphopenia was serious; all were characterized by the investigator to have been of mild or moderate intensity.

Further analyses were conducted to evaluate whether an association was apparent between the reductions observed in absolute lymphocyte count and risk for infection. The frequency of infection-related AEs and the type of infections (including those traditionally associated with T-cell dysfunction) reported among saxagliptin-treated subjects with non-isolated declines in lymphocyte count were similar compared with saxagliptin-treated subjects in the overall population. In an analysis of infection-related

AEs traditionally associated with T-cell dysfunction (eg, herpes virus, cytomegalovirus, tuberculosis) across the entire Phase 2b/3 clinical program, the frequency of these selected infection-related AEs were comparable between subjects who received saxagliptin and comparator treatment regimens. Thus, while the clinical significance of the decrease in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant infection-related adverse events.

5.2.6.2 Thrombocytopenia

The results from the Phase 3 clinical studies demonstrate no clinically meaningful or consistent effect on platelet counts (Section 3.2 of Module 2.7.4).[10]

In the Phase 2b study, there was a trend toward decreased platelet counts in the dose range of 5 mg and higher, which appeared to resolve after discontinuation of study medication. As a consequence of this finding, platelet counts were monitored frequently in the Phase 3 program. Treatment algorithms, including protocol mandated criteria for discontinuation and study drug interruption based on platelet count were implemented to guide investigators in cases where decreased platelets were noted. Pre-defined lists of AEs were developed to identify and gather additional information on these events in an ongoing manner.

In a pooled analysis of five Phase 3 placebo-controlled studies, comparable reductions from baseline in mean platelet count were observed in all treatment groups, including placebo. The magnitude of the decrease was approximately 2% from a baseline platelet count of 260,000 cells/μL. AEs of thrombocytopenia (see Section 2.3.5 of Module 2.7.4) were of low frequency across all treatment groups.[10]

In an outlier analysis, saxagliptin was associated with a modest increase in the number of subjects reaching a pre-defined threshold of ≥ 10% reduction in platelet count in most, but not all, data sets. The number of subjects reaching the pre-defined thresholds of ≥ 20% or ≥ 30% reduction in platelet count was generally comparable between saxagliptin and comparator.

There was one SAE of thrombocytopenia in a saxagliptin-treated subject reported as being due to myelodysplastic syndrome. However, based on hematology consultation as

requested by the investigator, the subject was considered to have a presumptive diagnosis of idiopathic thrombocytopenia pupura (ITP). The event was considered to be unlikely related to study drug by the Sponsor. Overall, there is no evidence that there is an effect of saxagliptin treatment on platelet count that is of clinical importance.

5.2.6.3 Liver Function Tests

There were no safety signals related to drug-induced liver injury based on analysis of changes from baseline, marked abnormalities, shift tables and combinations of liver function tests (eg, ALT or AST > 3x ULN with concomitant total bilirubin > 2x ULN; see Section 3.3 of Module 2.7.4).[10] In the five pooled placebo-controlled monotherapy and add-on combination studies, and in the initial combination study with metformin, the overall frequency of LFT abnormalities was low and similar between the saxagliptin and placebo treatment groups. There was no evidence of a dose-related response in LFT abnormalities seen in the Phase 3 studies.

5.2.6.4 Other Laboratory Tests

There was no evidence for effects on other hematology or chemistry parameters associated with saxagliptin treatment.

5.2.7 Relevance and Applicability of Safety Data for Dosing

In an extensive Phase 2b/3 program, saxagliptin administered at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo. Although the rate of isolated AEs was higher in subjects who received saxagliptin 10 mg compared with the 2.5 and 5 mg groups, dosing at saxagliptin 10 mg was also well tolerated, providing an additional safety margin for the saxagliptin 5 mg dose.

The comparability of the clinical safety profile of saxagliptin 2.5 mg and 5 mg was observed for overall AEs, SAEs, deaths, commonly reported AEs, and all events of special interest, except for those related to lymphocyte counts. There was a small, numerically higher rate of discontinuations due to AEs in the saxagliptin 5 mg compared with the 2.5 mg group, with no single AE preferred term predominating.

At a saxagliptin dose of 5 mg, a small decrease from baseline in mean absolute lymphocyte count of approximately 100 cells/μL relative to placebo was observed based on a pooled analysis of five placebo-controlled clinical studies. In contrast, saxagliptin 2.5 mg was generally indistinguishable from placebo with respect to effects on lymphocyte count. The clinical significance of the decrease in lymphocyte count associated with saxagliptin 5 mg relative to placebo is not known, although detailed assessments have not revealed any relevant clinical consequence.

In Study CV181013, there was an increased frequency of pedal edema in subjects who received 5 mg saxagliptin in combination with TZD compared with placebo + TZD and saxagliptin 2.5 mg + TZD. Edema is well described in subjects who receive an insulinotropic agent in conjunction with a TZD. These events were reported as mild to moderate in intensity and did not lead to study discontinuation. Whether the observation of pedal edema in Study CV181013 reflects a dose dependent effect or variability in reporting across treatment groups of TZD related edema is uncertain. The observation of increased numerical frequencies of some AEs in the saxagliptin 2.5 mg compared with 5 mg group is indicative of the variability in AE reporting.

In the add-on to glyburide study CV181040, the overall incidence of hypoglycemia was higher for the saxagliptin 2.5 and 5 mg doses versus placebo, without any dose-response. The overall incidence of hypoglycemia was similar in subjects treated with saxagliptin and control in the other Core Phase 3 studies. Based on these studies, there is no clear indication for a dose-response relationship with hypoglycemia.

Overall, in the extensive Phase 2b/3 program in 3422 subjects treated with saxagliptin, the safety profiles of saxagliptin 2.5 mg and 5 mg were generally comparable.

5.3 Limitations of the Saxagliptin Safety Database

The saxagliptin Phase 2b and 3 program was designed to enroll a broad population of subjects with T2DM, while optimizing the safety in subjects treated with an investigational agent. Experience in subjects ≥ 75 years of age is limited, as previously described (see Section 1.2.3). Exclusion criteria related to baseline renal function was primarily guided by the widespread use of metformin. Therefore, only approximately 1% of subjects in the Phase 3 program had moderate renal impairment at baseline, defined as

CrCl ≥ 30 to < 50 mL/min. No subject had severe renal impairment at baseline, defined as CrCl < 30 mL/min, and approximately 15% of subjects had mild renal impairment at baseline, defined as CrCl ≥ 50 to ≤ 80 mL/min. As a consequence, clinical experience in subjects with moderate or more severe renal impairment in the current Phase 3 program is limited.

Based on the single-dose study in subjects with renal impairment, a dose adjustment algorithm was derived from the pharmacokinetic characteristics of saxagliptin and the major metabolite. The algorithm was supported by the efficacy of the saxagliptin 2.5 mg dose, as well as the safety and tolerability profile of doses greater than 5 mg. Because there is a need for a single dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of saxagliptin and periodically thereafter. To provide additional information on the clinical safety and efficacy of saxagliptin and the steady-state pharmacokinetics of saxagliptin and BMS-510849 in subjects with T2DM with moderate, severe, or end-stage renal disease, a 12-week study of saxagliptin with a long-term extension in this population has been initiated and is currently ongoing.

Saxagliptin has not been evaluated in children, in subjects treated with insulin, in immunocompromised individuals (eg, subjects who have undergone organ transplantation or were diagnosed with human immunodeficiency virus), in subjects with congestive heart failure defined as NYHA III/IV and/or known left ventricular ejection fraction of ≤ 40%, or in pregnant or lactating women.

Saxagliptin, in repeated dosing, has not been studied in subjects with clinical evidence of active liver disease or ALT > 2 times the ULN, in subjects with severe and end-stage renal disease, or in subjects receiving potent CYP3A4 inhibitor or inducer agents.

Based on these limitations, appropriate warnings and precautions are included in the proposed label.

6 BENEFITS AND RISKS CONCLUSIONS

6.1 Summary of Benefits

The results from the eight clinical studies in the saxagliptin Phase 2b and 3 program in over 4600 subjects combined with the results from clinical pharmacology studies support the oral dose of saxagliptin 5 mg once daily in a wide range of subjects with T2DM, as either monotherapy, add-on combination therapy with metformin, a TZD, or a SU, or initial combination therapy with metformin.

In the Phase 2b dose-ranging study, administration of saxagliptin 5 mg was associated with significant inhibition of plasma DPP4 activity at the trough of the dosing interval as well as clinically meaningful decreases in A1C, fasting serum glucose and postprandial serum glucose. The results from the Phase 3 studies confirmed clinically meaningful benefits of saxagliptin 5 mg on A1C, as well as FPG, postprandial glucose, insulin, C-peptide, glucagon levels, and β-cell function. The results also demonstrated that treatment with saxagliptin resulted in a high percentage of subjects being able to achieve glycemic goals including A1C levels < 7%. Sustained effect relative to placebo was observed with up to 102 weeks of treatment. Saxagliptin treatment consistently demonstrated a beneficial antihyperglycemic effect across subgroups of demographic and baseline diabetes characteristics. In elderly subjects (≥ 65 years of age), A1C reductions and AE profiles were comparable to those in younger subjects, supporting a positive benefit:risk ratio in the elderly.

There was no consistent evidence that the 10 mg saxagliptin dose provided any incremental efficacy benefit over that observed with the 5 mg dose. Subjects in the saxagliptin 5 mg groups consistently demonstrated better glycemic control than subjects in the saxagliptin 2.5 mg group. Specifically:

- The saxagliptin 5 mg treatment groups demonstrated greater reductions from baseline in A1C than the saxagliptin 2.5 mg groups in four of five Phase 3 studies (note that Study CV181039 did not contain a saxagliptin 2.5 mg dose group). Similarly, maximal A1C benefit in the Phase 2b dose-ranging study was seen at a saxagliptin dose of 5 mg.

- The proportion of subjects who achieved A1C reductions ≥ 0.7% was greater in subjects who received saxagliptin 5 mg compared with 2.5 mg in four of five Phase 3 studies.
- There was a greater reduction from baseline in postprandial glucose AUC, which closely reflects the primary incretin-based mechanism for saxagliptin, for the saxagliptin 5 mg groups compared with the 2.5 mg groups in all Phase 3 studies.
- The proportion of subjects achieving a glycemic response of A1C < 7% was larger in the saxagliptin 5 mg groups compared with the 2.5 mg groups in four of five Phase 3 studies.

These observations demonstrate that saxagliptin 5 mg per day is the optimally efficacious dose.

6.2 Summary of Risks

Once-daily, orally-administered saxagliptin was safe and well-tolerated at doses of up to 400 mg QD for 2 weeks, 100 mg QD for 6 weeks, 40 mg QD for 12 weeks, and at 2.5, 5, and 10 mg QD for up to 102 weeks. In an extensive Phase 2b/3 program, saxagliptin given at doses of 2.5 and 5 mg was associated with an overall clinical AE profile that was comparable to placebo. Although the rate of certain AEs was higher in subjects who received saxagliptin 10 mg compared with those who received 2.5 and 5 mg, saxagliptin 10 mg was also safe and well tolerated, providing a safety margin for the saxagliptin 5 mg dose.

Long-term dosing of saxagliptin in the Phase 3 program, which included exposure up to 102 weeks in duration, did not reveal any unexpected events or emergent safety signals when compared with analyses of the short-term (24-week) study periods. The overall profile of AEs associated with extended dosing of saxagliptin for up to 2 years was consistent with that seen at 24 weeks.

A number of measures were implemented to monitor and collect information on specific events of special interest to complement standard safety monitoring. The events of interest included: (1) hypoglycemia; (2) events related to skin lesions; (3) selected infections (eg, events related to herpes simplex virus or Mycobacterium tuberculosis); (4) decreased lymphocyte counts; (5) decreased platelet counts; and (6) events of localized edema. Extensive analyses were also conducted to evaluate CV events, abnormalities in

liver function tests, and hypersensitivity reactions. In general, the safety profile for saxagliptin given at doses of 2.5 and 5 mg were indistinguishable and similar to the safety profile of placebo for these events of special interest, except for those related to lymphocyte counts.

Treatment with saxagliptin led to rates of hypoglycemia that were generally similar compared to placebo. This is consistent with the mechanism of action of DPP4 inhibitors, which exert their insulinotropic effects at the level of the β-cell in a glucose-dependent manner. However, the rate of hypoglycemia was numerically higher in subjects who received 2.5 or 5 mg of saxagliptin added on to an intermediate dose of glyburide compared with up-titration of glyburide monotherapy plus placebo. The difference in hypoglycemia rates between the saxagliptin treatment arms and placebo was not statistically significant. SUs, alone and in combination with other antihyperglycemic agents, are known to cause hypoglycemia, and decreases in SU dose may be warranted for certain subjects to reduce the risk of hypoglycemia.

The proportion of subjects with AEs of localized edema was generally similar in subjects who received saxagliptin and placebo. A higher rate of pedal edema was observed in subjects who received 5 mg saxagliptin in combination with TZD compared with placebo. Dependent edema, however, is well described in subjects who receive a TZD as monotherapy or in combination with other oral diabetes treatments. Further, the events of peripheral edema observed in subjects treated with saxagliptin added-on to TZD were mild to moderate in intensity and did not lead to study discontinuation. In this combination and in all other saxagliptin Phase 3 studies, there was no evidence for increased frequency of edema limited to the hands, which was specifically described as a dose-limiting effect in healthy subjects who received another member of the DPP4 inhibitor class[56]. The safety risk for this specific finding is low based on available data.

At a saxagliptin dose of 5 mg, a small decrease in mean absolute lymphocyte count from baseline was observed. While the mechanism for the decrease in lymphocyte count is unknown, further investigation did not show any evidence of impairment in lymphocyte proliferation, apoptosis / necrosis, and did not suggest that any one lymphocyte subtype was disproportionately affected during the time of decrease. While the clinical significance of the decrease in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant adverse events. There was no

evidence for an association of saxagliptin treatment with an increased risk of elevation of liver function tests or of elevation of serum creatinine.

In summary:

- The clinical safety profile of saxagliptin has been consistently confirmed across a large and diverse development program with few potential risks. The few potential risks were not associated with any clinical consequences.
- The overall clinical AE profile was comparable between the saxagliptin 2.5 and 5 mg doses and similar to that of placebo.
- The increased incidence of hypoglycemia when saxaglipitin is administered in combination with SU, the increased incidence of peripheral edema when saxaglipitin is given in combination with TZD, and the observation of a decrease in lymphocyte count are described in the proposed label.

6.3 Conclusions

In subjects with T2DM, treatment with saxagliptin compared with control treatment resulted in significantly improved glycemic control with a low risk of hypoglycemia. Saxagliptin treatment at 5 mg was well tolerated with an overall clinical AE profile similar to placebo. No serious adverse events of clinical relevance to the administration of saxagliptin were observed.

The efficacy and safety data demonstrate that 5 mg once daily dosing of saxagliptin provides the optimal glycemic benefit. The 10 mg saxagliptin dose did not provide incremental efficacy benefit over that observed with the 5 mg dose, while the 2.5 mg dose of saxagliptin consistently provided less glycemic benefit than the 5 mg dose. Given the comparable safety profile of the 2.5 mg dose and the 5 mg dose, the 5 mg once-daily dose of saxagliptin provides the optimal benefit:risk ratio in subjects with T2DM and is the recommended usual clinical dose in patients with normal renal function.

In subjects with mild renal impairment, exposure to both saxagliptin and BMS-510849 is less than 2-fold that observed in subjects with normal renal function. Accordingly, a dose of 5 mg saxagliptin in subjects with mild renal impairment is recommended. A dose of 2.5 mg saxagliptin in moderate and severe renal impairment is associated with saxagliptin exposures that are similar to the expected usual clinical dose of 5 mg in subjects with

normal renal function, and will result in exposures to BMS-510849 that approach the exposures typically achieved with a 10 mg dose in subjects with normal renal function. Thus, a 2.5 mg daily dose in moderate and severe renal impairment provides optimal benefit while maintaining systemic exposures to parent and metabolite within the current long-term clinical safety experience.

Saxagliptin represents a new treatment option for T2DM, a disease with many currently available treatments, but one that is increasing in prevalence and where many patients do not achieve satisfactory glycemic control. Saxagliptin provides clinically meaningful glycemic benefits, with an overall AE profile similar to placebo, when given as monotherapy, add-on therapy with metformin, TZDs, and SUs as well as in initial combination use with metformin, when treatment with dual saxagliptin and metformin therapy is appropriate.

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