

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-350

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	22-350	<i>Submission Date(s)</i>	6/30/08, 10/24/08, 11/19/08, 11/24/08, 12/2/08, 1/26/09
<i>Brand Name</i>	Onglyza		
<i>Generic Name</i>	Saxagliptin; BMS-477118		
<i>Reviewers</i>	Jayabharathi Vaidyanathan, Ph.D. Immo Zdrojewski, Ph.D.		
<i>Team Leader (Acting)</i>	Wei Qiu, Ph.D.		
<i>PM Reviewer</i>	Justin Earp, Ph.D.		
<i>PM Team Leader</i>	Christoffer Tornoe, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-2		
<i>OND Division</i>	Division of Metabolic and Endocrine Products		
<i>Sponsor</i>	Bristol-Myers Squibb		
<i>Relevant IND(s)</i>	63,634		
<i>Submission Type; Code</i>	Original 505 (b) (1) NME	(1)	S
<i>Formulation; Strength(s)</i>	Immediate release tablets; 2.5 mg and 5 mg		
<i>Indication</i>	Treatment of Type 2 diabetes		

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1 Executive Summary

Saxagliptin belongs to the DPP-4 inhibitor class of anti-diabetic agents. Januvia (sitagliptin) is the first approved DPP-4 inhibitor (NDA 21-995; approval date, Oct 16, 2006) by the FDA and the Agency.

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Saxagliptin is intended to improve glycemic control for patients with type 2 diabetes mellitus (T2DM). Sponsor is proposing saxagliptin 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 also as initial combination with metformin, as an adjunct to diet and exercise, when treatment with dual saxagliptin and metformin therapy is appropriate.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-350 for Onglyza (saxagliptin) and finds it acceptable provided that the Agency and the sponsor agree on the labeling. The recommendation and the following comments should be sent to the sponsor as appropriate.

- It is recommended to reduce the dose to 2.5 mg when co-administered with strong CYP3A4/5 inhibitors.
- Labeling comments on page 47.

Required office level OCP briefing was held on Thursday, March 26 2009 and the attendees were Drs. Chandra Sahajwalla, Suresh Doddapaneni, Wei Qiu, Hylton Joffe, Naomi Lowy, Fred Alavi, Todd Bourcier, Joga Gobburu, Mehul Mehta, Atik Rahman, Gil Burckhart, Kellie Reynolds, Sally Choe, Jayabharathi Vaidyanathan, Justin Earp, Michael Pacanowski, Johnny Lau, Sang Chung, Ritesh Jain, Immo Zdrojewski and Yun Xu.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The clinical pharmacology of saxagliptin has been characterized in 27 studies in healthy volunteers and T2DM patients. In addition, there are 23 bioanalytical study reports, 17 *in*

in vitro metabolism/permeability studies, and one protein binding study. Based on these studies, saxagliptin demonstrates the following properties:

Pharmacokinetic/ Biopharmaceutics Properties

- Single dose and multiple dose pharmacokinetics of saxagliptin were similar and there was no accumulation after once-daily dosing for 14 days. Following repeated administration, steady-state trough levels on day 2 was similar to that on day 4. The median Tmax was between 1.5-2.0 h following the 2.5 and 5 mg dose. The elimination half-life in patients was 2.3 – 3.3 h. The pharmacokinetics of saxagliptin in T2DM patients was similar to that observed in healthy subjects. Overall the AUC and Cmax increased proportionally with dose in the dose range of 2.5 mg to 50 mg in T2DM patients and 40 mg to 400 mg in healthy volunteers. The following Tables 1 and 2 present the PK parameters of saxagliptin in healthy subjects and T2DM patients, respectively.

Table 1: Summary statistics of saxagliptin PK parameters in healthy subjects (Study 010)

Saxagliptin PK Parameter	Saxagliptin Dose	Study Day	
		Day 1 n=10 for 40 mg n=6 for all other doses	Day 14 n=10 for 40 mg n=6 for all other doses ^a
C _{max} (ng/mL) Geometric Mean (C.V. %)	40 mg	226 (40)	224 (53)
	100 mg	585 (19)	487 (14)
	150 mg	694 (25)	614 (19)
	200 mg	1207 (11)	985 (22)
	300 mg	1845 (20)	1630 (31)
	400 mg	2321 (18)	1863 (22)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	40 mg	739 (26)	800 (24)
	100 mg	1899 (18)	1598 (11)
	150 mg	2543 (11)	2532 (9)
	200 mg	4186 (15)	4090 (10)
	300 mg	6652 (22)	6339 (26)
	400 mg	8364 (14)	8532 (13)
A _I for AUC(TAU) Geometric Mean (C.V. %)	40 mg		1.08 (18)
	100 mg		1.05 (15)
	150 mg		1.00 (13)
	200 mg	N/A	0.99 (19)
	300 mg		0.98 (14)
	400 mg		1.02 (8)
T _{max} (h) Median (Min, Max)	40 mg	1.00 (0.75, 2.00)	0.88 (0.50, 2.00)
	100 mg	1.13 (0.50, 2.00)	1.50 (1.50, 2.00)
	150 mg	1.50 (0.50, 2.00)	1.25 (0.75, 2.00)
	200 mg	1.50 (0.50, 2.00)	1.50 (0.75, 2.00)
	300 mg	1.50 (1.00, 1.50)	1.75 (1.00, 2.00)
	400 mg	1.50 (1.00, 1.50)	1.50 (0.75, 2.00)
T-HALF (h) Mean (S.D.)	40 mg	2.29 (0.18)	2.46 (0.29)
	100 mg	2.32 (0.22)	3.03 (1.29)
	150 mg	2.27 (0.14)	2.69 (0.91)
	200 mg	2.25 (0.21)	3.58 (1.25)
	300 mg	2.88 (0.85)	5.38 (3.44)
	400 mg	3.79 (1.11)	5.48 (2.55)
%SUR Mean (S.D.)	40 mg	26 (6)	25 (10)
	100 mg	19 (5)	23 (8)
	150 mg	18 (5)	22 (8)
	200 mg	24 (9)	29 (8)
	300 mg	25 (3)	26 (8)
	400 mg	27 (10)	20 (10)

CLR (mL/min) Mean (S.D.)	40 mg	259 (77)	220 (78)
	100 mg	183 (56)	221 (90)
	150 mg	189 (54)	230 (82)
	200 mg	199 (69)	241 (36)
	300 mg	191 (68)	196 (37)
	400 mg	213 (80)	159 (91)

Table 2: Summary statistics of saxagliptin PK parameters in T2DM patients (Study 002)

Pharmacokinetic Parameter	BMS-477118 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
C _{max} (ng/mL) Geometric Mean (C.V. %)	2.5 mg	11 (34)	11 (27)	12 (23)
	5 mg	21 ^a (18)	23 (31)	25 (22)
	15 mg	94 (26)	87 (14)	39 (20)
	30 mg	122 (33)	141 (34)	141 (25)
	50 mg	206 (11)	211 (24)	218 ^b (13)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2.5 mg	33 (28)	34 (20)	34 (20)
	5 mg	77 ^a (25)	76 (18)	81 (20)
	15 mg	371 (19)	375 (18)	365 (25)
	30 mg	618 (40)	682 (42)	676 (38)
	50 mg	949 (17)	917 (14)	915 ^b (19)
A.I. for AUC(0-T) Geometric Mean (C.V. %)	2.5 mg		1.05 (16)	1.05 (12)
	5 mg		1.00 ^a (9)	1.06 ^a (5)
	15 mg		1.01 (5)	0.99 (15)
	30 mg		1.10 (7)	1.09 ^b (9)
	50 mg		0.97 (8)	1.04 ^b (2)
T _{max} (h) Median (Min, Max)	2.5 mg	1.50 (0.75, 2.00)	1.25 (1.00, 4.00)	1.50 (0.75, 2.00)
	5 mg	2.00 ^a (1.00, 3.00)	2.50 (1.50, 3.00)	2.00 (1.50, 4.00)
	15 mg	2.00 (0.75, 3.00)	2.00 (1.50, 2.00)	1.75 (1.00, 2.00)
	30 mg	3.00 (2.00, 4.00)	2.00 (2.00, 3.00)	2.00 (1.00, 3.00)
	50 mg	2.50 (1.00, 3.00)	1.50 (1.50, 3.00)	1.50 ^b (1.50, 3.00)
T _{1/2} (h) Mean (S.D.)	2.5 mg	3.84 (1.72)	3.67 ^a (1.43)	3.32 (1.11)
	5 mg	2.21 ^a (0.15)	2.35 (0.48)	2.33 ^a (0.24)
	15 mg	2.46 (0.50)	2.48 (0.40)	2.55 (0.35)
	30 mg	2.35 (0.40)	2.33 (0.30)	2.36 (0.35)
	50 mg	2.17 (0.27)	2.39 (0.34)	2.27 ^b (0.30)
%UR Mean (S.D.)	2.5 mg	14 (7)	14 (3)	12 (4)
	5 mg	12 ^a (7)	22 ^a (7)	13 (5)
	15 mg	22 (4)	21 (5)	22 (5)
	30 mg	25 (6)	24 (4)	25 (3)
	50 mg	18 (4)	14 (7)	12 ^b (5)
CLR (mL/min) Mean (S.D.)	2.5 mg	--	--	--
	5 mg	--	--	--
	15 mg	140 ^c (50)	149 ^c (47)	123 ^b (63)
	30 mg	196 ^a (57)	163 ^a (36)	175 ^a (40)
	50 mg	157 ^a (35)	124 (69)	116 ^b (70)

- The mean exposure of the major active metabolite, BMS-510849 was 1.7 - 3 fold and 4-7 fold higher than the parent in healthy subjects and T2DM patients, respectively. The molar ratio of BMS-510849 to saxagliptin was similar on Days 1, 7 and 14 within each dose. The median T_{max} was 3 h and the mean apparent terminal half-life was 3.6 h following 5 mg dose.
- Co-administration of a 10 mg tablet with a high fat meal resulted in a 27% increase in AUC of saxagliptin and a decrease in exposure of BMS-510849 (C_{max} decreased by 18%). The median T_{max} of saxagliptin was prolonged from 0.53 h to 0.99 h, while the median T_{max} of BMS-510849 increased from 1.47 h to 1.98 h when saxagliptin was administered following a high-fat meal. The sponsor is requesting biowaiver for conducting additional clinical food effect

studies with the proposed 2.5 mg and 5 mg tablets and to apply the findings from the 10 mg food effect study to these lower strength tablets. The biowaiver is acceptable. Sponsor's proposed administration of saxagliptin regardless of food is acceptable.

- The serum protein binding for saxagliptin and BMS-510849 was negligible in plasma.
- A mass balance study indicates approximately 75% of the radioactivity recovered in the urine and about 22% in feces. The major metabolite observed in plasma was BMS-510849.
- A single dose study in renal impaired subjects indicated that renal function affected saxagliptin exposure significantly. Saxagliptin mean AUC increased by 15%, 40%, and 110% (2.1 fold) in subjects with mild, moderate, and severe renal impairment respectively, as compared to that of control subjects. C_{max} also increased by 39%, 7%, and 38% in subjects with mild, moderate, and severe, respectively, compared to that of subjects with normal renal function. Compared to subjects with normal renal function, ESRD subjects had 15%, 21% and 23% lower mean C_{max}, AUC_{inf} and AUC_(0-T) values of saxagliptin, respectively. Compared to subjects with normal renal function, subjects with mild, moderate, severe renal function and ESRD had 40%, 47%, 46%, and 36% , respectively, higher mean C_{max} values of BMS-510849 and 67%, 191% (2.9-fold), 347% (4.5-fold), and 306% (4.1-fold), respectively, higher mean AUC_(0-T) values of BMS-510849. The sponsor has proposed 2.5 mg for moderate, severe and ESRD patients and no dosage adjustments are being proposed for mild renal impairment. This is acceptable.
- Saxagliptin is predominantly metabolized in the liver by CYP3A4/5 and the exposure is expected to increase in hepatic impaired subjects. Compared to matched healthy subjects, there was a trend towards higher exposure for saxagliptin and lower exposure for BMS-510849 with increasing severity of hepatic impairment, indicating a reduced capacity to metabolize saxagliptin as hepatic function declines. For subjects with severe hepatic impairment, compared to matching healthy subjects, geometric mean C_{max} of saxagliptin was 6% lower and geometric mean AUC_{inf} and AUC_(0-T) was 77% and 72% higher, respectively. No dosage adjustments are proposed based on hepatic impairment. This is acceptable.
- Elderly subjects had higher systemic exposures to saxagliptin (approximately 60%↑) and BMS-510849 (35%↑) compared to young subjects. Adjustment for CL_{cr} and body weight reduced the saxagliptin PK difference between elderly and young to 12%, 29% and 30% for C_{max}, AUC_{inf} and AUC_(0-T), respectively. There was interaction between age and sex on saxagliptin exposure as indicated by 84-87% increase in elderly females as compared to young males. There was simultaneously about 68-70% increase in BMS-510849 exposure in elderly female subjects. No dosage adjustments are proposed by the sponsor based on age and gender. This is acceptable.
- Race did not have an effect on the clearance of saxagliptin based on population pharmacokinetic analysis.

- Saxagliptin is a CYP3A4/5 substrate as well as a P-glycoprotein substrate. The effect of strong CYP3A inhibitors and inducers on saxagliptin concentrations is an important issue.
 - Drug interaction was evaluated with the following: ketoconazole, diltiazem, rifampicin, maalox Max, famotidine, omeprazole, glyburide, pioglitazone, metformin, digoxin and simvastatin. The most significant changes in the saxagliptin exposure occurred in presence of metabolic modulators. The DDI with ketoconazole was conducted with 100 mg and 20 mg saxagliptin and there was about 2.5-fold and 3.8-fold increase in saxagliptin exposure, respectively. The extent of increase in exposure of saxagliptin 5 mg in presence of ketoconazole is unknown. In addition, considering the adverse events that resulted in presence of ketoconazole, it is recommended to reduce the dose to 2.5 mg when patients will be prescribed strong CYP3A4/5 inhibitors. In addition, there was a statistical decrease in C_{max} of saxagliptin in the presence of Maalox max (26% ↓) and metformin (21% ↓). The 90% CI for these fell outside of the 80-125% limit for C_{max} in presence of these drugs with no impact on the AUC of saxagliptin. This change is not likely to be clinically significant.
 - Induction of CYP3A4/5 by rifampin caused an 80% decrease in saxagliptin exposure. Although this was not associated with corresponding increase in BMS-510849 exposure, there was about 40% increase in its C_{max}. Induction also resulted in a decrease in saxagliptin half life from 3.02 to 1.7 h. This metabolic induction is also evident in a 5-fold increase in the metabolite-to-parent AUC ratio. The clinical significance of these changes is unknown. However, if the exposure of the total active moiety (molar parent exposure + one half molar metabolite exposure) is considered, there was about 25% decrease in the total exposure, which is unlikely to cause an clinically significant changes.
- The final to-be-marketed tablets were similar to the formulation used in phase 3 trials except for the color and embossing. Saxagliptin molecule contains chiral centers. Chiral conversion was examined and there was no conversion *in vivo*.

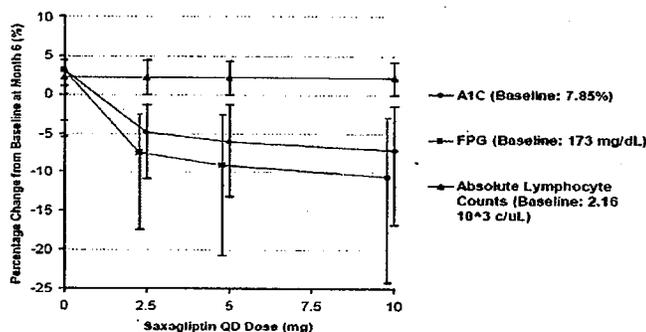
Exposure (Dose)-Response Relationship

- The thorough QT study shows saxagliptin does not prolong QT_c based on the concentration-dQT_c relationship, with doses up to 8-fold of the therapeutic dose.
- Dose-response relationship shows that the HbA_{1c} lowering effect was increased with increase in dose from 2.5 mg to 5 mg QD.
- Dosing with saxagliptin appeared to have a dose-dependent effect on plasma DPP-4 activity. As expected, DPP-4 inhibition was negligible for subjects receiving placebo. For subjects receiving saxagliptin, DPP-4 inhibition peaked, on average, between 1.5 and 6 hours after dosing. The amount remaining inhibited at the end of the dose interval (24 h) was 37% and 65% at the proposed clinical dose of 2.5 mg and 5 mg respectively.
- The exposure-efficacy response modeling for A1C LOCF after 24 weeks of saxagliptin administration at QD doses of 2.5, 5, and 10 mg showed that the

reduction of A1C was linearly related to the log of AUCT, the total active moiety exposure after saxagliptin administration. Model identified significant covariates on the A1C were baseline A1C and duration of T2DM. For subjects (with duration of T2DM of 3 months, baseline A1C of 8%) receiving saxagliptin 5 mg QD treatment for 24 weeks, the expected A1C (95th prediction interval) was predicted to be 7.34 (7.23 - 7.46) %.

- The exposure-safety response modeling on the absolute lymphocyte counts after 6 months of saxagliptin administration at QD doses of 2.5, 5, and 10 mg showed that the decrease of absolute lymphocyte counts is linear to the increase of the total active moiety exposures within the tested QD dose range of 2.5-10 mg, however the magnitude of the change, approximately 4% placebo-adjusted decrease for subjects receiving 5 mg QD treatment of 6 months is unlikely to be clinically relevant. Exposure-safety response modeling did not find a correlation between the platelet counts and serum creatinine concentration to the total active moiety exposure after 6 months of saxagliptin administration at QD doses of 2.5, 5, and 10 mg. It was concluded that the responses of platelet counts and serum creatinine concentration after 6 month of saxagliptin administration at QD doses of 2.5, 5, and 10 mg were not found to be related to the saxagliptin administration.
- Based on the results of the population pharmacokinetic analyses and the exposure-response analyses, the efficacy outcomes (A1C and FPG) and safety outcome (absolute lymphocyte counts) after 6 months of saxagliptin treatment were predicted at given saxagliptin regimen and relevant covariates (baseline A1C, duration of T2DM, baseline body weight, baseline absolute lymphocyte counts). The predicted outcomes were transformed into the percent change from baseline, and the summary statistics of the percent change from baseline is presented in Figure 1. It shows that as saxagliptin dose increases, the reduction of A1C and FPG from baseline is expected to increase, with overlapping prediction intervals at 2.5, 5, and 10 mg. There is a slight decrease of absolute lymphocyte counts as dose increases, but the magnitude is unlikely to be clinically relevant, as the predicted decrease of absolute lymphocyte counts after 6 months of saxagliptin treatment at 5 mg QD dose is only about 4% more than the predicted value for placebo treatment.

Figure 1. Model Predicted Efficacy and Safety Outcomes after 6 Months of Saxagliptin Treatment. Solid symbols and vertical bars represent the median and 95% prediction intervals.



- *Lymphocyte count:* 14 of 15 subjects experienced a decline in lymphocyte count on Day 10 following administration of a single dose of 100 mg saxagliptin + 200 mg ketoconazole q12h (study 005). In another study (022), following administration of a single 20 mg dose of saxagliptin one week earlier, co-administration of a second single dose of 20 mg saxagliptin and 200 mg ketoconazole q12h dosed to steady-state resulted in a decrease (30.6%) in absolute lymphocyte counts. The levels returned to baseline levels within 72 h. Overall, there was a decrease in lymphocyte count when saxagliptin was co-administered with ketoconazole as well as when there was an interrupted dosing of saxagliptin.

Overall, the cumulative data regarding the clinical pharmacology of saxagliptin support the proposed use of this drug in T2DM patients.

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Saxagliptin (Onglyza) is a new chemical entity developed by BMS for the indication of treatment of type 2 diabetes. Saxagliptin belongs to a new class of drugs known as DPP-4 (dipeptidyl peptidase-4) inhibitors. Currently only one DPP-4 inhibitor (Januvia) is approved in the USA. A standard review status was granted for this NDA.

2.1.2 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

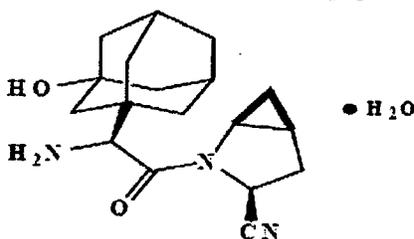
Saxagliptin drug substance is a

For the initial clinical studies (up to the end of Phase 2b), drug substance in (designated as _____) was employed in the clinical development program. A capsule dosage form containing the _____ of saxagliptin _____ was developed and used to evaluate the initial safety and pharmacokinetics of saxagliptin. Subsequently, drug substance, as the _____ monohydrate (designated as _____) was selected for further development. Saxagliptin drug products developed for Phase 3 clinical studies were film coated immediate release tablets in three strengths: 2.5 mg, 5 mg and 10 mg (calculated as the _____). These tablets differed from the early clinical tablets in the amount and color of coating material.

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Saxagliptin is a chiral molecule with four stereogenic centers (*S,S,S,S* configuration), two being fixed in relative stereochemistry as part of the cyclopropane ring. The presence of two of the diastereomers (BMS-573659 and BMS-644448) in human plasma and urine samples from human ADME study as well as from late stage clinical trials were re-examined for the presence of radioactivity or MS signal at the retention times corresponding to the standards. In both conditions, no signals were detected at the retention times of BMS-573659 and BMS-644448.

Figure 2: Structure of saxagliptin



2.1.3 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Saxagliptin is an orally active inhibitor of DPP-4 enzyme intended for the treatment of type 2 diabetes in adults. Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

DPP-4 is found free in the plasma and as a cell surface enzyme mainly located on vascular endothelium and on epithelial cells in a variety of organs. It is the enzyme primarily responsible for the degradation and inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) which play a critical role in glucose homeostasis. Inhibition of DPP-4 prolongs the life of these polypeptide hormones in the circulation leading to improving glucose dependent insulin secretion and reduction of inappropriate glucagon secretion. These hormones contribute to the control of postprandial glucose excursions in a glucose dependent manner, mitigating the risk of hypoglycemia.

In addition to enhancing postprandial insulin release, GLP-1 also reduces glucagon release from the pancreatic α -cells, thereby reducing hepatic glucose production. 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.

In vitro enzymological assays using the chromogenic dipeptide gly-pro-pNA pseudo substrate and the endogenous GLP-1 substrate, with recombinant human DPP-4 indicated that saxagliptin exhibited a K_i value of 1.3 ± 0.3 nM. Saxagliptin is metabolized to BMS 510849, a monohydroxylated metabolite that is present in human plasma at levels 2 to 7 \times the level of the parent drug. This metabolite is also an inhibitor of DPP4, and is 2x less potent than saxagliptin, and has a K_i of 2.6 ± 1.0 nM. Saxagliptin and BMS-510849 exhibited selectivity (391 and 948 \times , respectively) for DPP4 over DPP8, and (75 and 163 \times , respectively) for DPP4 over DPP9 at 37 $^{\circ}$ C. Saxagliptin had a K_i for inhibition of

plasma DPP activity of 1.7 nM (IC₅₀ 13 nM) and 0.9 nM (IC₅₀ 9 nM) in human and cynomolgus monkey plasma, respectively.

2.1.4 What are the proposed dosage and route of administration?

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

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Twenty-seven (27) clinical pharmacology studies were conducted in healthy volunteers as well as type 2 diabetic patients. The studies include

- Single ascending dose, multiple ascending dose, and ADME mass balance studies.
- Special populations PK study (renal impairment, hepatic impairment, age and gender).
- Drug-drug interaction studies.
- Pharmacodynamic studies investigating saxagliptin's effect on DPP-4 inhibitory activity.
- Effect of saxagliptin on cardiac QT interval.
- Relative bioavailability studies.

In addition, there are 23 bioanalytical study reports, 17 in vitro metabolism/permeability studies, and one protein binding study.

In the dose-ranging study, doses in the range of 2.5 mg – 40 mg were evaluated for 12 weeks. 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. The different phase 2b-3 trials to support dosing claims are summarized in the table below.

Table 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%)	425 / 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 / 305*	24 weeks (205 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 (205 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

2.2.2 *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The American Diabetes Association (ADA) recommends the use of HbA1c levels as an indicator of glycemic control. The sponsor has used the change from baseline in HbA1c at the end of double-blind treatment as the primary efficacy variable in all key efficacy studies. In addition, PD parameters based on the mechanism of action of drug were measured in some clinical pharmacology studies. They include DPP-4 enzyme activity, levels of GLP-1, GIP, insulin, glucagon, and glucose.

2.2.3 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

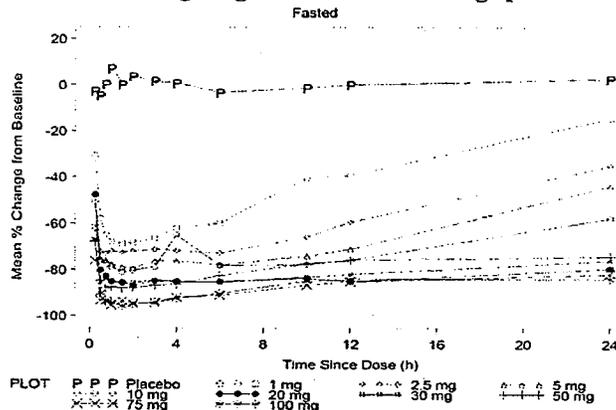
Yes. Please refer to the Analytical section for details.

2.2.4 *What are the characteristics of the exposure-response relationship (dose response, concentration-response)?*

- **Efficacy**

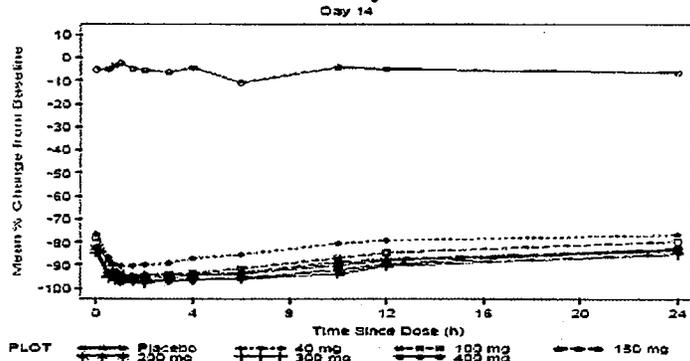
Effect of saxagliptin on DPP-4 inhibition: Saxagliptin inhibited plasma DPP-4 activity in a dose-dependent manner. The pharmacodynamic effect of saxagliptin was investigated in normal volunteers as well as T2DM patients. Following single dose administration (study 001) in healthy subjects, maximum of 73% and 79% inhibition was achieved during the first 0.75 – 2 h after administration of saxagliptin at doses 2.5 mg and 5 mg, respectively. Inhibition was 35% and 44% after 24 h post-dose following 2.5 mg and 5 mg dose, respectively (Figure 3).

Figure 3: Plot of Mean Percent Changes from Baseline for Plasma DPP-4 Activity following single oral dose of saxagliptin



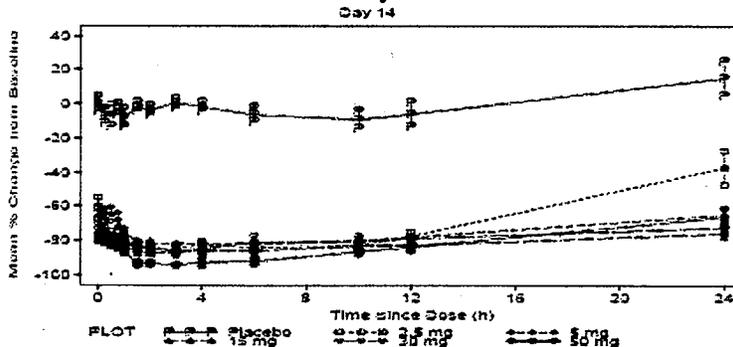
Following multiple dose administration (study 010) in healthy subjects, the DPP-4 inhibition peaked, on average, between 0.75 and 4 hours after dosing on both Day 1 and Day 14. Plasma DPP-4 inhibition on Days 1 and 14 appeared to be dose-dependent both in terms of the maximum inhibition and the amount remaining inhibited at the end of the dose interval (24 h) from 40 to 150 mg QD saxagliptin. Dosing with saxagliptin at 100, 150, 200, 300 and 400 mg resulted in larger inhibition of plasma DPP-4 activity than dosing with saxagliptin 40 mg, no clear difference was observed between the 150 mg – 400 mg doses. For all doses, plasma DPP-4 activity was inhibited by at least 74% at 24 hours after a single dose and following two weeks of daily dosing. The peak inhibition of plasma DPP-IV activity on Days 1 and 14 was between 1 and 2 h post-dose which tended to coincide with the Tmax values for both saxagliptin and BMS-510849 (Figure 4).

Figure 4: Plot of Mean Percent Changes from Baseline for Plasma DPP-4 Activity on Day 14



Following multiple dose administration (study 002) in T2DM patients, the plasma DPP-4 inhibition was dose-dependent. As expected, DPP-4 inhibition was negligible for subjects receiving placebo. For subjects receiving saxagliptin, DPP-4 inhibition peaked, on average, between 1.5 and 6 hours after dosing. The amount remaining inhibited at the end of the dose interval (24 h) was 37% and 65% at the proposed clinical dose of 2.5 mg and 5 mg respectively (Figure 5).

Figure 5: Plot of Mean Percent Changes from Baseline for Plasma DPP-IV Activity on Day 14



Plasma active GLP-1 concentrations: In general, dosing with saxagliptin (in the dose ranges of 40 to 200 mg) in healthy subjects produced an increase in mean changes from baseline (although not dose-dependent effect) for postprandial AUC(0-3h) plasma active GLP-1 over those observed for subjects on placebo for all meals.

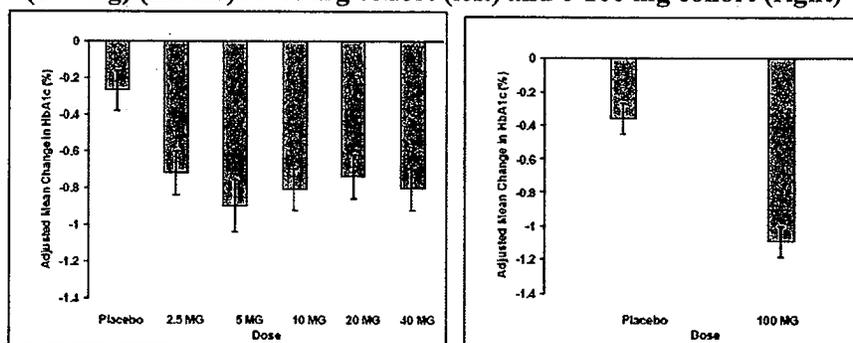
Saxagliptin did not appear to have a dose-dependent effect on plasma active GLP-1 concentrations in T2DM patients. For patients receiving saxagliptin, plasma active GLP-1 concentrations generally peaked, on average, at 6 hours after dosing. Exceptions were the 50 mg dose-group which produced plasma active GLP-1 concentrations which peaked, on average, at 1 hour after dosing on Days 1 and 14, and the 2.5 mg dose-group which produced plasma active GLP-1 concentrations which peaked, on average, at 45 minutes after dosing on Day 1.

Other PD parameters: Dosing with saxagliptin did not appear to have a dose dependent or time-dependent (day of dosing) effect on glucose over 24 hours from the time of dosing. Dosing with saxagliptin did not appear to have a dose-dependent or time-dependent effect on HOMA, glucose AUC0-4 values, serum insulin or C-peptide over 4 hours from the time of meal.

Effect on HbA1c:

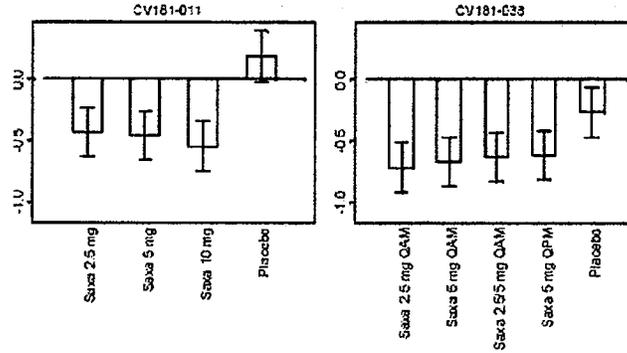
Dose finding: In the dose-finding study (008), the safety and efficacy of saxagliptin monotherapy in treatment-naïve subjects with T2DM who had inadequate glycemic control. Subjects were randomized to receive 1 of 5 doses of saxagliptin (2.5, 5, 10, 20, and 40 mg) or placebo once daily for 12 weeks (0-40 mg cohort). An additional 85 subjects were randomized to receive saxagliptin 100 mg or placebo once daily for 6 weeks (0,100 mg cohort). The results indicate that the largest effect on glycemic control (decreases in HbA1c, fasting plasma glucose and postprandial serum glucose) was generally seen at a dose of 5 mg or 10 mg, with no apparent increase in efficacy at doses higher than 10 mg in the 0-40 mg cohort (Figure 6). There was also significant inhibition of plasma DPP-4 activity at trough (24 h post-dose), with the largest effect seen at 10 mg, with no apparent increases at doses higher than 10 mg. On this basis, once-daily regimens of 2.5, 5, and 10 mg saxagliptin administered to subjects with T2DM were characterized in the core phase 3 studies.

Figure 6: Adjusted mean change (SE) from baseline in HbA1c at week 12 or week 6 (100 mg) (LOCF): 0-40 mg cohort (left) and 0-100 mg cohort (right)



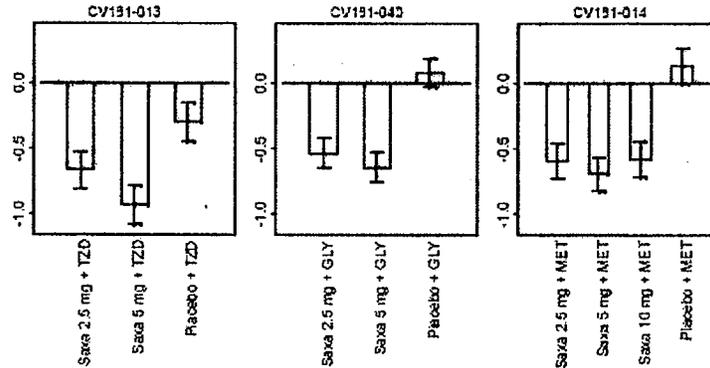
Phase 3 studies: The primary endpoint in the core studies (011, 038, 013, 014, 040 and 039) was the change in HbA1c from baseline to week 24. Statistically significant reductions from baseline in HbA1c were seen across all studies in the saxagliptin treatment group compared to control. Treatment with 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 (Figure 7 & 8). There was no consistent evidence for incremental efficacy benefit at 10 mg beyond that seen for 5 mg. Similar overall glycemic lowering efficacy was achieved when the saxagliptin 5 mg dose was given in the morning (QAM) and evening (QPM) in study 038 (Figure 7).

Figure 7: HbA1c adjusted mean changes from baseline (95%CI) at Week 24 (LOCF) - Phase 3 monotherapy studies



Studies 013, 014, and 040 evaluated the safety and efficacy of saxagliptin in combination with thiazolidinedione (TZD), metformin, or sulfonylurea (SU), respectively, in subjects with inadequate glycemic control on TZD, metformin, or SU alone (Figure 8). Study 039 evaluated the safety and efficacy of saxagliptin in combination with metformin as initial therapy versus initial therapy with saxagliptin or metformin as monotherapies.

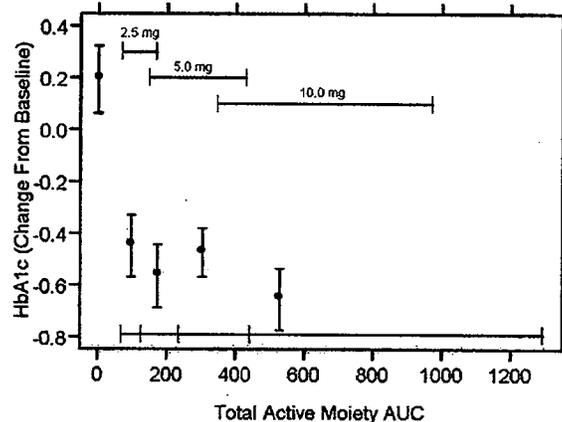
Figure 8: HbA1c adjusted mean changes from baseline (95%CI) at Week 24 (LOCF) - Phase 3 add-on combination therapy studies



Exposure-response: Figure 9 indicates there is a difference in response between subjects who received saxagliptin or placebo. However, the effect appears to have reached its maximum response in patients whose exposures were within 2.5 mg dose range. Exposure response relationships may be more evident for doses less than 2.5 mg. Dosing 10 mg over 5 mg will likely offer no improvement in HbA1c reduction. Dosing 5 mg over 2.5 mg may not offer improvement in response at week 24.

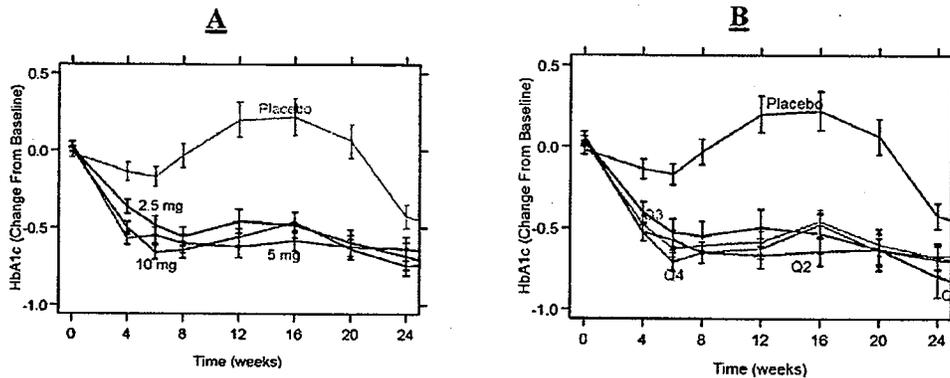
Figure 9: Exposure Response Relationship for HbA1c Change from Baseline at Week 24. Mean HbA1c change from baseline for each quartile of exposures (AUC) are plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety for each dose are plotted as lines

indicating the range of response for the expected distribution of AUC values within each dose. The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.



Efficacy of Saxagliptin was monitored at various weeks over the duration of the phase 3 clinical trials. In study 11 subjects who received placebo or 2.5, 5, or 10 mg of saxagliptin for 24 weeks. Figure 10 shows that there is no dose-response for effectiveness in study 11 above the 2.5 mg dose (Panel A) and that this is also not exposure dependent (Panel B). No distinction can clearly be made between the time course of response when grouped by dose or exposure (indicated by quartiles, Q1-Q4).

Figure 10. Time-course of HbA1c response by dose (Panel A) and exposure quartile (Panel B). Data and error bars are plotted as mean \pm SEM.



The sponsor's proposed dose of 5 mg is acceptable. No benefit was observed from 10 mg over 5 mg in Figure 9 or 10.

- **Safety**

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),

hypersensitivity reactions, localized edema of the hands and feet, abnormalities in liver function test, increased reports of infections, and increases in serum creatinine.

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.

Effect on lymphocyte count: 14 of 15 subjects experienced a decline in lymphocyte count on Day 10 following administration of a single dose of 100 mg saxagliptin + 200 mg ketoconazole q12h (study 005). Pyrexia, chills, and decreased lymphocytes appeared after the second dose of 100 mg saxagliptin, which was administered 8 days after the first 100 mg dose of saxagliptin in this study. The second 100 mg dose was co-administered with ketoconazole doses to steady-state which suggests the combination of saxagliptin and ketoconazole may be implicated in the appearance of pyrexia, chills and lymphocyte findings.

In another study (022), following administration of a single 20 mg dose of saxagliptin one week earlier, co-administration of a second single dose of 20 mg saxagliptin and 200 mg ketoconazole q12h dosed to steady-state resulted in a decrease (30.6%) in absolute lymphocyte counts. The levels returned to baseline levels within 72 h.

Study 031 assessed the role of the interrupted dosing of saxagliptin on the lymphocyte changes. Absolute lymphocyte count decreases were observed on Day 23 in subjects administered placebo on Day 1, 40 mg saxagliptin QD from Day 2 through Day 15, placebo from Day 16 through Day 22 and a single dose of 40 mg saxagliptin on Day 23 (Sequence 2).

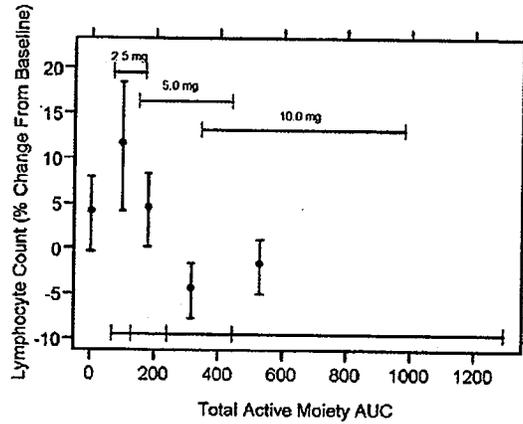
Reviewer's comments: Overall, there was a decrease in lymphocyte count when saxagliptin was co-administered with ketoconazole as well as when there was an interrupted dosing of saxagliptin. The effect of following 5 mg QD dose in the above scenario as well as the clinical significance of this change is not known.

Exposure-safety: Lymphocyte count, platelet count, and serum creatinine concentrations were plotted to examine for correlation with saxagliptin exposure.

Lymphocyte count: Lymphocyte response to saxagliptin exposure is shown in Figure 11. The greatest reduction in lymphocyte count (4% at 24 weeks) was observed for exposures relevant to 5 mg or higher saxagliptin. While these exposures are possible at the proposed dosing regimen, a 4% reduction in lymphocyte count may not have clinically significant/symptomatic effects at 24 weeks.

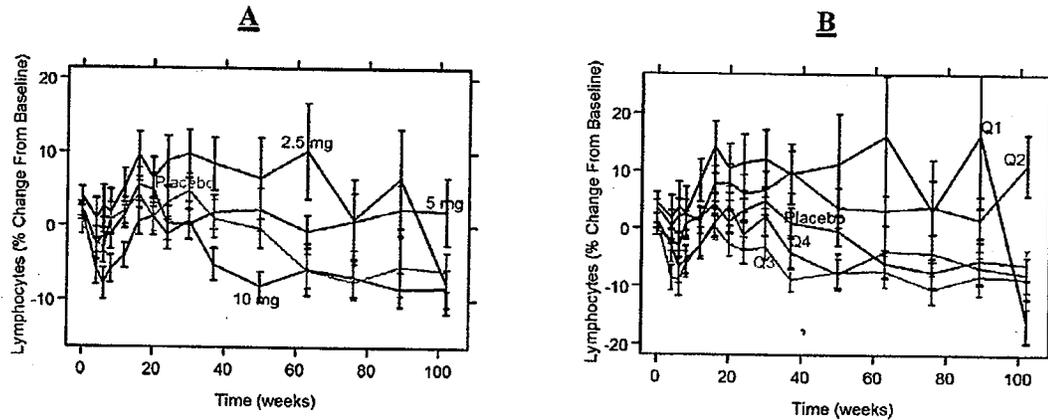
Figure 11. Exposure Response Relationship for Lymphocyte Count. *Mean percent change from baseline in lymphocyte count at week 24 for each quartile of exposures (AUC) are plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety for each dose are plotted as lines indicating the range of response for the expected distribution of AUC values within each dose.*

The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.



There appears to be a dose dependent response and that the response for the 5 mg dose is not significantly different from placebo. However, the 10 mg dose shows reduction is as great as 10% change from baseline (Figure 12).

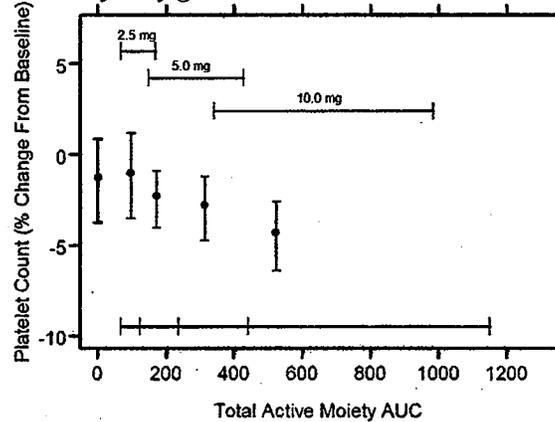
Figure 12. Time-course of lymphocyte response by dose (Panel A) and exposure quartile (Panel B). Data and error bars are plotted as mean \pm SEM.



Platelet count. Platelet count response to saxagliptin exposure is shown in Figure 13. Platelet count appears to slowly decrease with increasing saxagliptin exposure. The exposures achieved at the proposed 5-mg dose may cause a slight reduction in platelets at week 24. Exposures from the 5- and 10-mg doses could reduce platelet count by as much as 5% at week 36.

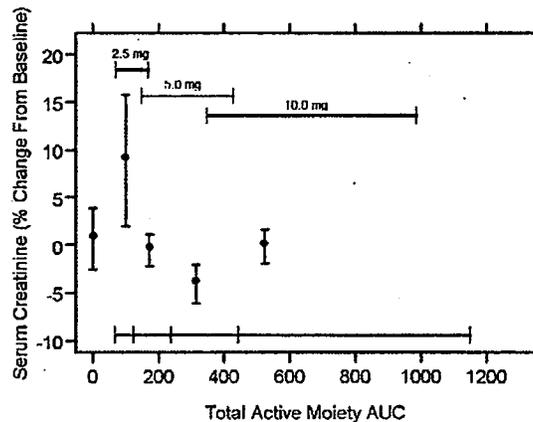
Figure 13: Exposure Response Relationship for Platelet Count. Mean change from baseline in platelet count for each quartile of exposures (AUC) is plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety for each dose are plotted as lines indicating

the range of response for the expected distribution of AUC values within each dose. The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.



Serum creatinine. There is no apparent change in serum creatinine in response to saxagliptin exposures (Figure 14).

Figure 14. Exposure Response Relationship for Serum Creatinine. Mean percent change from baseline in serum creatinine for each quartile of exposures (AUC) is plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety for each dose are plotted as lines indicating the range of response for the expected distribution of AUC values within each dose. The range of exposures in each quartile is represented by the range of each segment of the solid red line at the bottom of the figure.



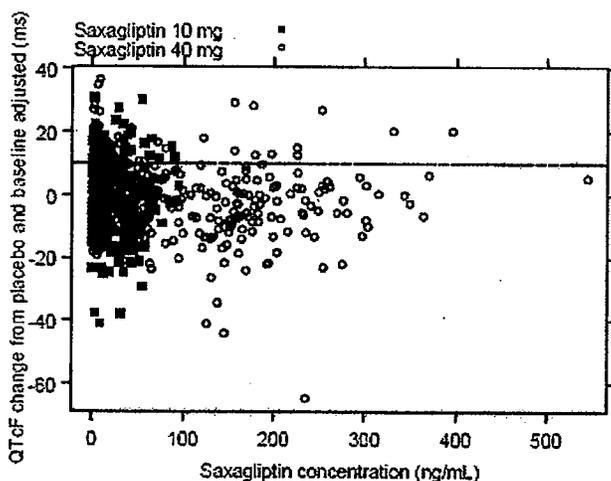
2.2.5 Does this drug prolong the QT or QTc interval?

The effect of saxagliptin on the QT interval was assessed in a randomized, double-blind, four-period, four-treatment, multiple-dose, crossover study, in which 40 healthy subjects received saxagliptin 10 mg, saxagliptin 40 mg, and placebo once daily for 4 days.

Moxifloxacin (single-dose 400 mg) was used as a positive control. No significant effect of saxagliptin was detected in this 'thorough QT' study. The largest upper limits of the two-sided 90% CI for the mean difference between saxagliptin (10 and 40 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect a small effect on the QT interval.

The geometric mean C_{max} of saxagliptin on Day 4 was 235 ng/mL and 49 ng/mL following the 40 mg and 10 mg given QD for 4 days. This mean C_{max} is about 10-fold higher than the mean C_{max} at the therapeutic dose (~ 20-24 ng/mL at 5 mg). The relationship between $\Delta\Delta\text{QTcF}$ and saxagliptin concentrations is visualized in Figure 15 with no evident exposure-response relationship. Please see QT-IRT review under IND 63,634 for more details.

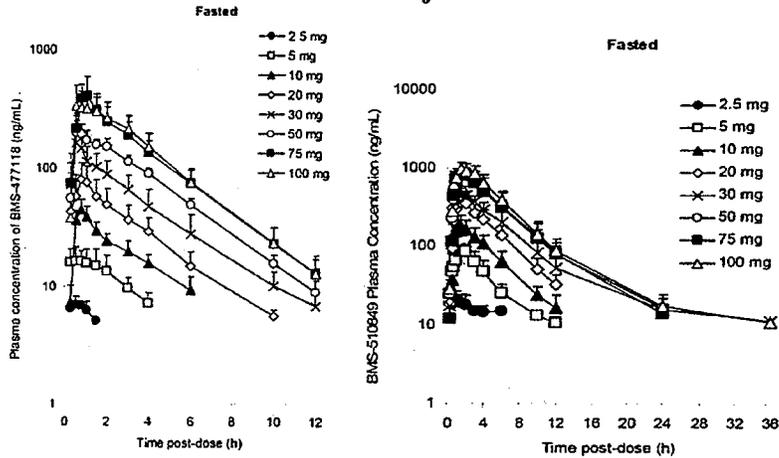
Figure 15: $\Delta\Delta\text{QTcF}$ versus saxagliptin concentration



2.2.6 *What are the single dose and multiple dose PK parameters in healthy subjects?*

Single oral doses in the range of 1-100 mg were administered in healthy volunteers. The median T_{max} ranged from 0.5 – 1.0 h and 1.0 – 2.0 h while the mean half-life ranged from 1.2 – 2.8 h and 2.8 – 6.7 h for saxagliptin and BMS-510849, respectively in the 1-100 mg dose range under fasting conditions.

Figure 16. Mean (plus SD) plasma concentration for saxagliptin (left) and BMS 510849 (right) following administration of single dose of 2.5 to 100 mg of saxagliptin to healthy subjects in fasted state.



Multiple doses of 40, 100, 150, 200, 300 and 400 mg were studied in healthy volunteers. The PK profiles of saxagliptin on Day 1 and Day 14 was similar (Table 4). There was no evidence of accumulation following once daily dosing for 2 weeks. There was also no evidence of saxagliptin inhibiting or inducing its own metabolism following daily oral doses of 40 to 400 mg for 2 weeks. Across the dose groups on Days 1 and 14, the mean amounts of a saxagliptin dose excreted into the urine (unchanged saxagliptin) ranged between 18 and 29%. In general, saxagliptin trough concentrations were similar on Day 2 and 4.

Both C_{max} and AUC_{tau} of BMS-510849 appeared to increase proportionally with saxagliptin doses up to 300 mg but appeared to increase less than proportionally at the 400 mg saxagliptin dose. Mean BMS-510849 urinary recoveries was 21 and 33% of the saxagliptin dose over a dose interval. Across the dose groups on Days 1 and 14, the mean BMS-510849 plasma exposures on a molar basis were between 1.7 and 3.0-fold higher than parent saxagliptin.

Table 4: Summary Statistics of Saxagliptin PK Parameters in healthy subjects following single dose and multiple dose administration

Saxagliptin PK Parameter	Saxagliptin Dose	Study Day	
		Day 1 n=10 for 40 mg n=6 for all other doses	Day 14 n=10 for 40 mg n=6 for all other doses ^a
C _{max} (ng/mL) Geometric Mean (C.V. %)	40 mg	226 (40)	224 (33)
	100 mg	585 (19)	487 (14)
	150 mg	694 (25)	614 (19)
	200 mg	1207 (11)	985 (22)
	300 mg	1845 (20)	1630 (31)
	400 mg	2321 (18)	1663 (22)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	40 mg	739 (26)	800 (24)
	100 mg	1899 (18)	1668 (11)
	150 mg	2548 (13)	2532 (9)
	200 mg	4186 (15)	4080 (10)
	300 mg	6652 (22)	6539 (26)
	400 mg	8364 (14)	8532 (13)
A.I. for AUC(TAU) Geometric Mean (C.V. %)	40 mg		1.08 (15)
	100 mg		1.05 (15)
	150 mg		1.00 (13)
	200 mg	N/A	0.99 (19)
	300 mg		0.98 (14)
	400 mg		1.02 (8)
T _{max} (h) Median (Min, Max)	40 mg	1.00 (0.75, 2.00)	0.88 (0.50, 2.00)
	100 mg	1.13 (0.50, 2.00)	1.50 (0.50, 2.00)
	150 mg	1.50 (0.50, 2.00)	1.25 (0.75, 2.00)
	200 mg	1.50 (0.50, 2.00)	1.50 (0.75, 2.00)
	300 mg	1.50 (1.00, 1.50)	1.75 (1.00, 2.00)
	400 mg	1.50 (1.00, 1.50)	1.50 (0.75, 2.00)
T-1/2 _λ (h) Mean (S.D.)	40 mg	2.29 (0.18)	2.48 (0.29)
	100 mg	2.32 (0.22)	3.03 (1.29)
	150 mg	2.27 (0.14)	2.69 (0.91)
	200 mg	2.25 (0.21)	3.58 (1.25)
	300 mg	2.58 (0.85)	5.38 (3.44)
	400 mg	3.79 (1.11)	5.48 (2.55)

2.2.7 How does the PK of saxagliptin and its major active metabolite, BMS-510849 in T2DM patients compared to that in healthy volunteers?

The PK characteristics of saxagliptin and BMS-510849 were similar in healthy subjects and type 2 DM patients.

The PK profiles of saxagliptin (2.5, 5, 15, 30 and 50 mg) administered once daily for 14 days in T2DM patients were similar for Days 1, 7 and 14 and there was no accumulation. The mean apparent terminal elimination half life appeared to be similar (2.2 – 3.3 h) up to 50 mg dose range in T2DM patients. The median T_{max} was 1.5 – 2 h.

Table 5: Summary Statistics of saxagliptin Pharmacokinetic Parameters in T2DM patients following single dose and multiple dose administration

Pharmacokinetic Parameter	BMS-177113 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
C _{max} (ng/mL) Geometric Mean (C.V. %)	2.5 mg	11 (34)	11 (27)	12 (23)
	5 mg	21 ^a (18)	23 (31)	23 (22)
	15 mg	94 (26)	87 (14)	39 (20)
	30 mg	122 (33)	141 (34)	141 (25)
	50 mg	206 (11)	211 (24)	218 ^b (13)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2.5 mg	33 (28)	34 (20)	34 (20)
	5 mg	77 ^a (25)	76 (18)	31 (20)
	15 mg	371 (19)	375 (18)	365 (25)
	30 mg	618 (40)	682 (42)	676 (38)
	50 mg	949 (17)	917 (14)	915 ^b (19)
A.I. for AUC(0-T) Geometric Mean (C.V. %)	2.5 mg		1.03 (16)	1.05 (12)
	5 mg		1.00 ^a (9)	1.06 ^a (5)
	15 mg		1.01 (5)	0.99 (35)
	30 mg		1.10 (7)	1.09 (9)
	50 mg		0.97 (8)	1.04 ^b (2)
T _{max} (h) Median (Min, Max)	2.5 mg	1.50 (0.75, 2.00)	1.25 (1.00, 4.00)	1.50 (0.75, 2.00)
	5 mg	2.00 ^a (1.00, 3.00)	2.50 (1.50, 3.00)	2.00 (1.50, 4.00)
	15 mg	2.00 (0.75, 3.00)	2.00 (1.50, 2.00)	1.75 (1.00, 2.00)
	30 mg	3.00 (2.00, 4.00)	2.00 (2.00, 3.00)	2.00 (1.00, 3.00)
	50 mg	2.50 (1.00, 3.00)	1.50 (1.50, 3.00)	1.50 ^b (1.50, 3.00)
T _{1/2} (h) Mean (S.D.)	2.5 mg	3.84 (1.72)	3.67 ^a (1.43)	3.32 (1.11)
	5 mg	2.21 ^a (0.15)	2.35 (0.48)	2.33 ^a (0.24)
	15 mg	2.46 (0.50)	2.48 (0.40)	2.55 (0.35)
	30 mg	2.35 (0.40)	2.33 (0.30)	2.36 (0.35)
	50 mg	2.17 (0.27)	2.39 (0.34)	2.27 ^b (0.20)
%UR Mean (S.D.)	2.5 mg	14 (7)	14 (5)	12 (4)
	5 mg	12 ^a (7)	22 ^a (7)	13 (5)
	15 mg	22 (4)	21 (5)	22 (5)
	30 mg	25 (6)	24 (4)	25 (3)
	50 mg	18 (4)	14 (7)	12 ^b (5)

Similarly, there was no difference in the PK profiles of BMS-510849 on Days 1, 7, and 14. The molar ratio of metabolite:parent was similar on Days 1, 7, and 14 within each dose. The apparent terminal half-life was also not changed on Days 7 and 14 as compared to Day 1. The mean exposure of BMS-510849 was 4-7 fold higher than the parent in T2DM patients.

2.2.8 What are the characteristics of drug absorption?

The absolute bioavailability of saxagliptin was not determined. The AUC and C_{max} increased linearly following single and multiple dose administration in the dose range of 2.5 – 400 mg (see dose-proportionality below). The time to reach C_{max} ranged from 1.5 - 4 hours (Study 002) following 5 mg dose given once daily for 14 days in type 2 diabetic patients. Absorption was slightly delayed in the presence of food (by 30 min, see food effect).

In vitro permeability of saxagliptin was determined in Caco-2 cells and the permeability was found to be 18 nm/sec which was comparable to compounds that exhibited poor absorption (12%) in humans. In the mass balance study in healthy subjects 74.9% of dose

(% total radioactivity) was in the urine and the exposure of the main metabolite BMS-510849 was 3.1 times higher than the parent drug.

2.2.9 *What are the characteristics of drug distribution?*

The serum protein binding for saxagliptin and metabolite BMS-510849 was negligible in all species tested. The concentration of parent and metabolite in the serum protein binding assay was 100 ng/mL.

Table 6: Free Fraction (%) of saxagliptin and BMS-510849 in Mouse, Rat, Dog, Monkey and Human Serum (Mean ± SD, n=3)

	Mouse	Rat	Dog	Monkey	Human
BMS-477118	73.3 ± 21.5	82.0 ± 1.5	109.0 ± 30.2	79.6 ± 25.5	107.9 ± 34.2
BMS-510849	109.7 ± 16.6	104.0 ± 8.4	97.8 ± 19.5	89.4 ± 3.0	103.1 ± 24

2.2.10 *Does the mass balance study suggest renal or hepatic as the major route of elimination?* (reviewed by Dr. Zdrojewski)

Saxagliptin is eliminated by both renal and hepatic pathways.

Saxagliptin (23.53%) and BMS-510849 plus other minor monohydroxylated metabolites (35.74%) account for 59.27% of the administered dose excreted in urine. The remaining 15.6% account for other minor metabolites. The mean apparent renal clearance of saxagliptin in this study (234 mL/min) suggests active renal secretion.

A mean of 22.05% of the administered saxagliptin dose was recovered in feces. Intact saxagliptin accounted for only 0.5% in the feces. The mean recovery of saxagliptin drug related material in urine and feces combined in the initial 24 h after dosing was 71.4% and 13.93% respectively. The overall mean radioactivity in subjects was 97.05% indicating complete recovery (Table 7).

Table 7: Listing of Individual Pharmacokinetic Parameters for TRA

Subject	%UR	%FE	%TOTAL
CV181004-1-1	↑		
CV181004-1-2			
CV181004-1-3			
CV181004-1-4			
CV181004-1-5			
CV181004-1-6			
Mean	74.90	22.05	97.05

b(4)

%UR=total percentage urinary excretion, %FE=total percentage fecal excretion
* values excluded from analysis due to incomplete urine collection for subject 6

2.2.11 What are the characteristics of drug metabolism?

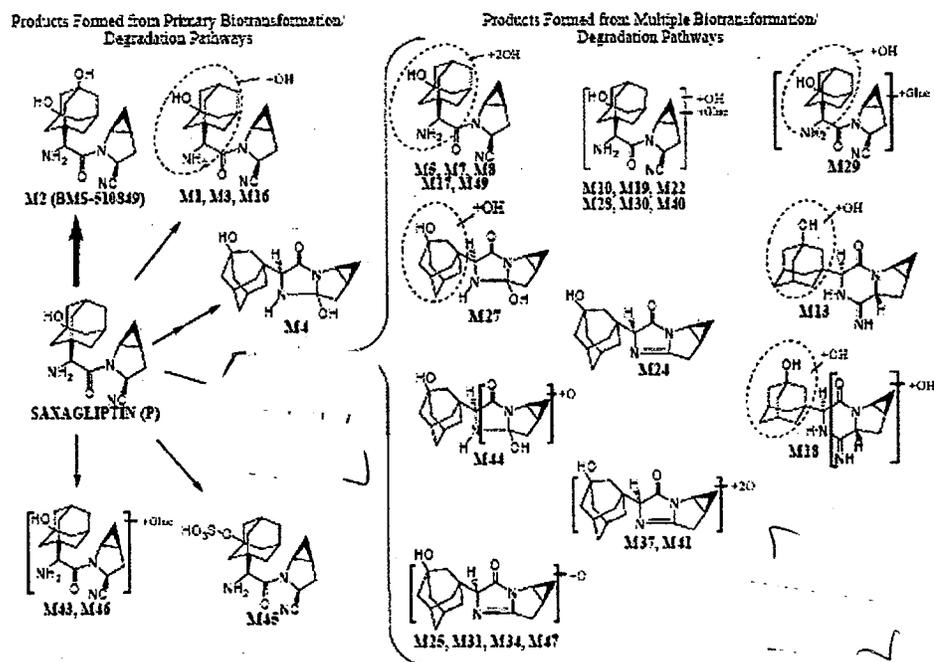
Saxagliptin is extensively metabolized. It is mainly hydrolyzed by CYP450 3A4/5 enzymes to form BMS-510849.

When saxagliptin was incubated with HLM in the presence of ketoconazole (1 μ M), a direct inhibitor of CYP3A4/5, or troleandomycin (20 μ M), a time-dependent inhibitor of CYP3A4/5, the formation of BMS-510849 was inhibited by >97%. There was no inhibition with inhibitors of other CYP enzymes indicating that saxagliptin is a substrate of CYP3A4/5. In the presence of antibodies against other CYP enzymes (anti- 1A2, 2B6, 2C8, 2C19 and 2D6), the formation of BMS-510849 was not affected.

The proposed pathways for the *in vivo* biotransformation of [14 C]saxagliptin in rat, dog, monkey and human are illustrated in Figure 17. Overall, the *in vitro* metabolite profile of BMS-477118 was qualitatively similar in mouse, rat, dog and human liver microsomes as well as cDNA-expressed human CYP3A4 and CYP3A5. In all species studied, the major pathway for the metabolism of saxagliptin was hydroxylation of the adamantyl group to form metabolite M2 (BMS-510849). Minor pathways for the metabolism of saxagliptin observed in one or more of the species.

Figure 17:

Proposed pathways for the *in vivo* biotransformation of [14 C]saxagliptin in rats, dogs, monkeys and humans



b(4)

2.2.12 *What are the characteristics of drug excretion?*

Based on the mass balance study, saxagliptin is extensively metabolized. Renal elimination route was the major route of elimination of the metabolite, BMS-510849. 74.9% of the total radioactivity was excreted in urine. The mean elimination half life after multiple oral administrations in patients was between 2.3 – 3.3 h following 2.5 mg and 5 mg dose. Saxagliptin is almost completely eliminated within 24 h post dose.

2.2.13 *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

Dose proportionality was estimated using the power model, ($Y = \alpha \cdot \text{Dose}^\beta$ where Y, α and β correspond to the PK parameter (AUC or Cmax), proportionality constant and an exponent, respectively). If the 90% CI for the exponent β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional.

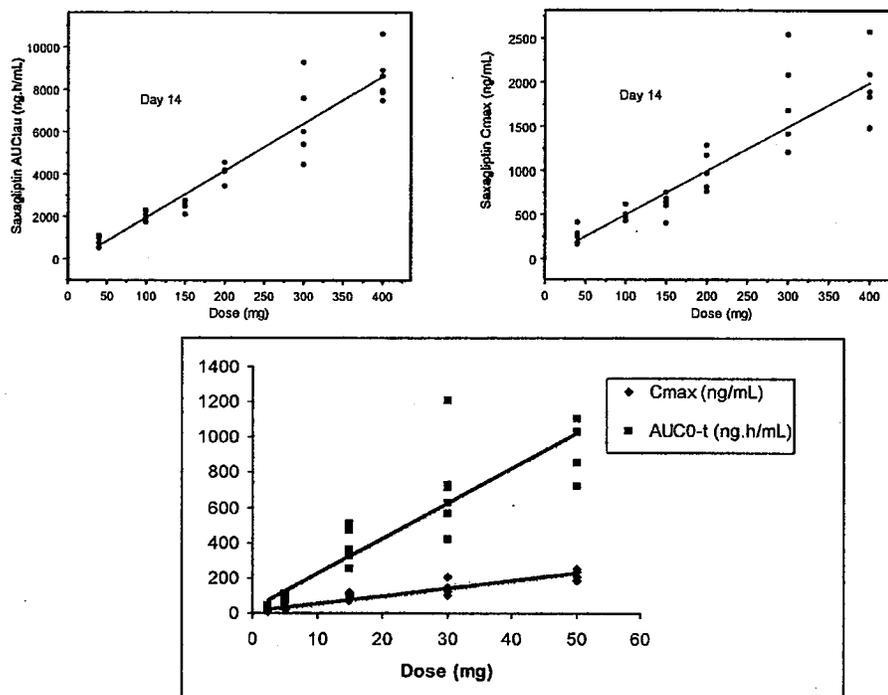
Dose-proportionality was examined using saxagliptin AUC and Cmax obtained from the multiple dose ascending studies in healthy volunteers and T2DM patients. Dose proportionality was demonstrated on all days (1, 7 and 14). Point estimates and 90% confidence intervals for the dose-proportionality parameter (slope of the linear regression) were calculated from the study 010 and are shown below:

- Cmax Day 1: 1.00 [0.84 – 1.17]
- Cmax Day 14: 0.95 [0.755 – 1.14]
- AUCinf Day 1: 1.06 [0.93 – 1.20]
- AUC τ Day 14: 1.03 [0.87 – 1.18]

The results slope (90%CI) for Ln Dose Vs. Ln (AUC) or Ln(Cmax) are as follows for T2DM patients (study 002):

- Cmax Day 1: 0.98 (0.71 – 1.25)
- Cmax Day 14: 0.976 (0.79 – 1.15)
- AUCinf Day 1: 1.14 (0.9 – 1.39)
- AUC0- τ Day 14: 1.13 (0.87 – 1.39)

Figure 18: Saxagliptin AUC_{0-t} and C_{max} on Day 14 in healthy volunteers (top) and T2DM patients (bottom)



2.2.14 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability of < 25% was noted in pharmacokinetic parameters of AUC and C_{max}. The population analysis estimated that the apparent clearance of saxagliptin had an inter-individual variability (%CV) of 7.3%.

Some of the studies that can be used to get an estimate of the inter-subject variability for AUC and C_{max} of saxagliptin are shown in Table 8.

Table 8: Variability estimates (%CV) for AUC and C_{max} of saxagliptin 5 mg dose.

Study		Inter-subject variability (%CV)	
		C _{max}	AUC _{0-t}
002	T2DM PK	22	20
001	Healthy PK	14.2	23.3
026	Healthy DDI (10 mg)	22	22

The between subject variability in the molar ratio (metabolite: parent) was relatively large, ranging from 18 to 47% CV. *In vitro* studies suggest CYP3A4/5 is the primary enzyme involved in BMS-477118 biotransformation to BMS-510849, and the between subject variability in the molar ratio probably reflects the between subject variability in CYP3A4/5 activity.

2.3 Intrinsic Factors

2.3.1 *What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

- Age and gender

The geometric means of C_{max} , AUC_{inf} and $AUC_{(0-T)}$ of saxagliptin were, respectively, 14%, 15% and 16% higher in female subjects than in male subjects. The geometric means of C_{max} , AUC_{inf} and $AUC_{(0-T)}$ of saxagliptin were, respectively, 23%, 59% and 61% higher in elderly than in young subjects. The sponsor concluded that the saxagliptin PK changes with age and gender were not clinically significant (Figure 19 & Table 9).

Figure 19: Saxagliptin AUC (left) and C_{max} (right) versus age and gender

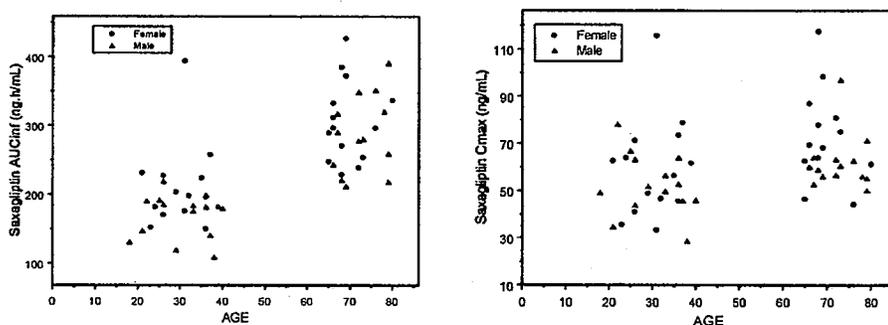


Table 9: Results of statistical analyses on saxagliptin PK parameters

Pharmacokinetic Parameter	Geometric Means		Female /Male Ratio of Geometric Means	
	Male	Female	Point Estimate	90% C.I.
C _{max} (ng/mL)	56	63	1.14	(1.01, 1.28)
C _{max} (ng/mL) - Adjusted for CL _{cr} and body weight	56	62	1.10	(0.98, 1.24)
AUC _(INF) (ng·h/mL)	215	248	1.15	(1.05, 1.27)
AUC _(INF) (ng·h/mL) - Adjusted for CL _{cr} and body weight	214	248	1.16	(1.05, 1.27)
AUC _(0-T) (ng·h/mL)	207	241	1.16	(1.06, 1.28)
AUC _(0-T) (ng·h/mL) - Adjusted for CL _{cr} and body weight	207	242	1.17	(1.06, 1.29)
Pharmacokinetic Parameter	Geometric Means		Elderly /Young Ratio of Geometric Means	
	Young	Elderly	Point Estimate	90% C.I.
C _{max} (ng/mL)	53	66	1.23	(1.09, 1.38)
C _{max} (ng/mL) - Adjusted for CL _{cr} and body weight	56	63	1.12	(0.90, 1.41)
AUC _(INF) (ng·h/mL)	183	291	1.59	(1.45, 1.75)
AUC _(INF) (ng·h/mL) - Adjusted for CL _{cr} and body weight	203	262	1.29	(1.08, 1.54)
AUC _(0-T) (ng·h/mL)	176	284	1.61	(1.46, 1.77)
AUC _(0-T) (ng·h/mL) - Adjusted for CL _{cr} and body weight	196	255	1.30	(1.08, 1.56)

The geometric means of C_{max}, AUC_{inf} and AUC_(0-T) of BMS-510849 were, respectively, 25%, 24% and 26% higher in female subjects than in male subjects. The geometric means of AUC_{inf} and AUC_(0-T) of BMS-510849 were, respectively, 35% and 36% higher in elderly than in young subjects. The geometric mean of C_{max} of BMS-510849 was however 7% lower in elderly than in young subjects (Figure 20 & Table 10).

Figure 20: BMS-510849 AUC (left) and C_{max} (right) versus age and gender

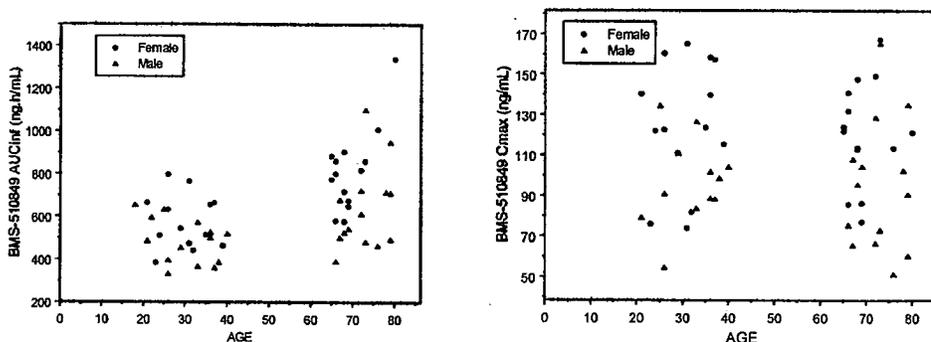


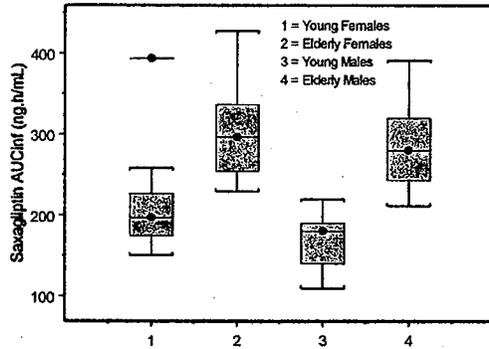
Table 10: Results of statistical analyses on BMS-510849 PK parameters

Pharmacokinetic Parameter	Geometric Means		Female / Male Ratio of Geometric Means	
	Male	Female	Point Estimate	90% C.I.
C _{max} (ng/mL)	96	119	1.25	(1.10, 1.42)
C _{max} (ng/mL) - Adjusted for CL _{cr} and body weight	97	117	1.20	(1.05, 1.37)
AUC _(INF) (ng·h/mL)	538	669	1.24	(1.12, 1.38)
AUC _(INF) (ng·h/mL) - Adjusted for CL _{cr} and body weight	535	672	1.26	(1.13, 1.39)
AUC _(0-T) (ng·h/mL)	520	654	1.26	(1.13, 1.40)
AUC _(0-T) (ng·h/mL) - Adjusted for CL _{cr} and body weight	518	657	1.27	(1.14, 1.41)
	Geometric Means		Elderly / Young Ratio of Geometric Means	
	Young	Elderly	Point Estimate	90% C.I.
C _{max} (ng/mL)	111	103	0.93	(0.82, 1.05)
C _{max} (ng/mL) - Adjusted for CL _{cr} and body weight	115	100	0.87	(0.68, 1.12)
AUC _(INF) (ng·h/mL)	515	697	1.35	(1.22, 1.51)
AUC _(INF) (ng·h/mL) - Adjusted for CL _{cr} and body weight	599	600	1.00	(0.82, 1.21)
AUC _(0-T) (ng·h/mL)	501	679	1.36	(1.22, 1.51)
AUC _(0-T) (ng·h/mL) - Adjusted for CL _{cr} and body weight	582	585	1.01	(0.83, 1.23)

Reviewer's Comments:

- Elderly subjects had higher systemic exposures to saxagliptin (approximately 60%) and BMS-510849 (35%) compared to young subjects. Adjustment for CL_{cr} and body weight reduced the saxagliptin PK difference between elderly and young to 12%, 29% and 30% for C_{max}, AUC_{inf} and AUC_(0-T), respectively. Since the majority of saxagliptin that is not cleared renally is likely to be metabolized, the balance of the difference in saxagliptin systemic clearance is probably due to a decreased metabolic capacity (intrinsic clearance and/or reduced hepatic blood flow) with increased age. Interestingly, the mean percentage of the saxagliptin dose recovered as BMS-510849 in the urine was similar between young and elderly subjects (30 and 29 %, respectively).
- There was interaction between age and sex on saxagliptin exposure as indicated by 84-87% increase in elderly females as compared to young males. There was simultaneously about 68-70% increase in BMS-510849 exposure in elderly female subjects. While, elderly males had about 20%, 72% and 74% increase in saxagliptin C_{max}, AUC_{inf} and AUC_(0-T) respectively as compared to young males and about 20% increase in AUCs of BMS-510849.

Figure 21: Saxagliptin exposure based on age and gender



- No dosage adjustments are proposed by the sponsor based on age and gender. This is acceptable.

• **Renal Impairment**

Renal function affected saxagliptin exposure significantly (Figure 22). Saxagliptin AUC increased by 15%, 40%, and 110% (2.1 fold) in subjects with mild, moderate, and severe renal impairment respectively, as compared to that of control subjects. C_{max} also increased by 39%, 7%, and 38% in subjects with mild, moderate, and severe, respectively, compared to that of normal subjects (Table 11). Compared to subjects with normal renal function, subjects on hemodialysis (saxagliptin dose administered prior to the day's dialysis session) had 15%, 21% and 23% lower geometric mean C_{max}, AUC_{inf} and AUC_(0-T) values of saxagliptin, respectively.

Figure 22: Saxagliptin AUC in renal impairment compared to normal subjects (left) and scatter plot of AUC versus CLcr (right)

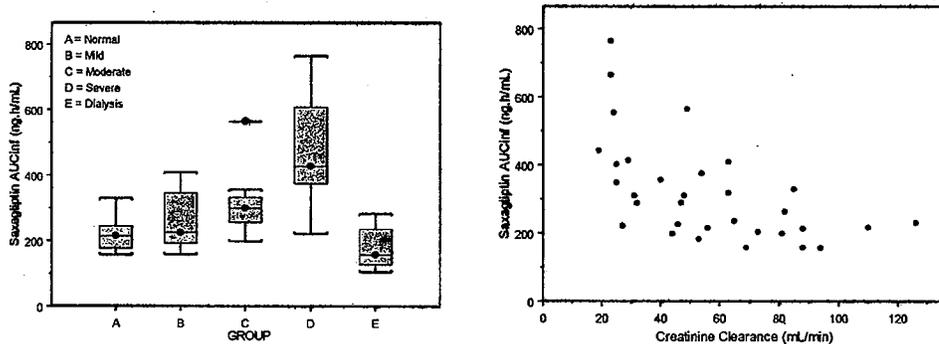


Table 11: Saxagliptin PK parameters in renal impairment

Saxagliptin Pharmacokinetic Parameter	Renal Function Group					
	Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	Severe (n=7*)	Hemodialysis (n=8)
C_{max} (ng/mL)						
Geo. Mean (CV%)	54 (25)	75 (26)	58 (36)	74 (35)	72 (38)	46 (35)
AUC_(0-T) (ng·h/mL)						
Geo. Mean (CV%)	215 (25)	249 (36)	303 (35)	447 (37)	434 (40)	170 (37)
AUC_(0-T) (ng·h/mL)						
Geo. Mean (CV%)	208 (26)	240 (36)	292 (35)	437 (37)	423 (41)	160 (40)
T_{max} (h)						
Median	0.63	0.88	1.50	1.00	1.00	0.83
(Min, Max)	(0.50, 1.50)	(0.25, 1.50)	(0.50, 5.00)	(0.50, 1.50)	(0.50, 1.00)	(0.50, 3.00)
T-half (h)						
Mean (SD)	3.09 (0.65)	3.50 (1.62)	4.02 (1.23)	4.42 (1.06)	4.41 (1.14)	3.39 (0.21)
CL_{T/F} (mL/min)						
Mean (SD)	796 (191)	705 (230)	572 (165)	399 (168)	414 (176)	1039 (358)
%UR or %DR (%)						
Mean (SD)	20 (4)	20 (6)	12 (9)	7 (3)	7 (4)	4 (1)
CLR (mL/min)						
Mean (SD)	153 (23)	131 (37)	61 (28)	26 (8)	25 (9)	Not applicable
CLD (mL/min)						
Mean (SD)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	91 (35)

Note: *Subject CV131019-1-26 was receiving nifedipine (CYP3A4 inhibitor) and hence excluded from the analysis. Since saxagliptin is a CYP3A4 substrate, nifedipine may have altered the PK of saxagliptin and the formation of BMS-510849.

%UR: Percent urinary recovery for subjects not on dialysis; %DR: Percent dialysate recovery for subjects on dialysis

Metabolite BMS0510849 exposure also significantly increased with renal impairment (Figure 23). Compared to subjects with normal renal function, subjects with mild, moderate, severe renal function and ESRD had 40%, 47%, 46%, and 36% , respectively, higher geometric mean C_{max} values of BMS-510849 and 67%, 191% (2.9-fold), 347% (4.5-fold), and 306% (4.1-fold), respectively, higher geometric mean AUC_(0-T) values of BMS-510849 (Table 12).

Figure 23: BMS-510849 AUC in renal impairment compared to normal subjects (left) and scatter plot of AUC versus CL_{cr} (right)

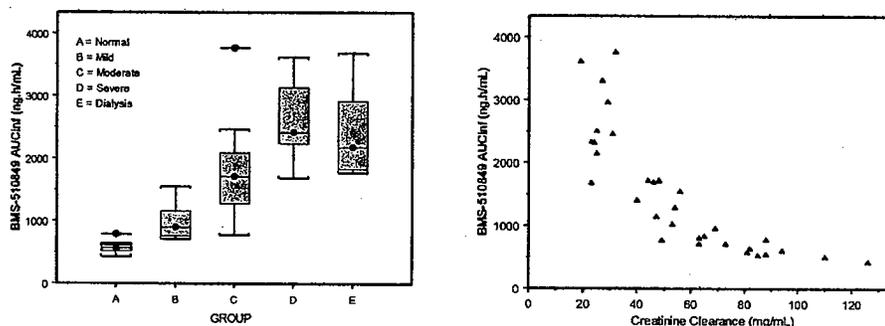


Table 12: BMS-510849 PK parameters in renal impairment

BMS-510849 Pharmacokinetic Parameter	Renal Function Group					Hemodialysis (n=3)
	Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	Severe (n=7*)	
C _{max} (ng/mL) Geo. Mean (CV%)	92 (32)	129 (26)	135 (35)	134 (31)	131 (34)	125 (37)
AUC(INF)(ng*h/mL) Geo. Mean (CV%)	569 (13)	930 (30)	1660 (50)	2541 (25)	2574 (26)	2330 (30)
AUC(0-T)(ng*h/mL) Geo. Mean (CV%)	555 (13)	929 (30)	1617 (51)	2479 (25)	2508 (27)	2257 (30)
T _{max} (h) Median (Min, Max)	1.25 (0.92, 2.00)	1.75 (1.00, 3.00)	4.00 (2.00, 8.28)	5.00 (2.00, 8.00)	5.00 (2.00, 8.00)	2.63 (2.00, 4.00)
T _{1/2} (h) Mean (SD)	3.85 (0.55)	5.33 (2.72)	8.55 (2.44)	9.59 (1.43)	9.88 (1.23)	12.51 (1.34)
%UR or %DR (%) Mean (SD)	27 (7)	29 (4)	25 (6)	20 (5)	19 (5)	19 (4)
CLR (mL/min) Mean (SD)	76 (11)	52 (17)	28 (13)	13 (3)	12 (3)	Not applicable
CLD (mL/min) Mean (SD)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	39 (21)

Note: *Subject CV181019-1-26 was on nifedipine (CYP3A4 inhibitor) and hence excluded from the analysis. Since saxagliptin is a CYP3A4 substrate, nifedipine may have altered the PK of saxagliptin and the formation of BMS-510849.

%UR: Percent urinary recovery for subjects not on dialysis; %DR: Percent dialysate recovery for subjects on dialysis.

Reviewer's Comments:

- The sponsor has proposed 2.5 mg for moderate, severe and ESRD patients and no dosage adjustments are being proposed for mild renal impairment.
- Although the parent exposure increase in mild impairment was not significantly different than normal subjects, the metabolite exposure increased by 70%. The molar ratio also increased with renal impairment (Table 13). Considering the pre-clinical studies where wide safety margin for saxagliptin (~ 50-fold) was observed, no dosage adjustment proposed for mild renal impairment appears to be reasonable.

Table 13: Saxagliptin and metabolite change in renal impairment

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

- **Hepatic impairment**

For the mild hepatic function group, the geometric means for saxagliptin C_{max}, AUC_{inf} and AUC_(0-T) for impaired subjects were 8%, 10% and 10% higher, respectively, compared to matching healthy subjects. Saxagliptin C_{max}, AUC_{inf} and AUC_(0-T) geometric means were 2%, 38% and 38% higher, respectively, for moderately impaired subjects compared to matching healthy subjects. For subjects with severe hepatic impairment, compared to matching healthy subjects, geometric mean C_{max} was 6% lower and geometric mean AUC_{inf} and AUC_(0-T) was 77% and 72% higher, respectively (Figure 24 & Table 14).

Figure 24: Saxagliptin exposure in different stages of hepatic impairment compared to matched controls

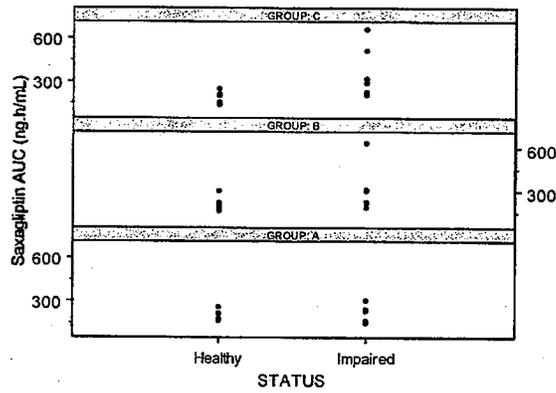


Table 14: Results of Statistical Analyses of Saxagliptin C_{max}, AUC(INF) and AUC(0-T)

Hepatic Function Group	Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
		Subject Status	Mean	Ratio	Point Estimate	90% Confidence Limits
A (Mild)	C _{max} (ng/mL)	Impaired	60	Impaired/Healthy	1.077	(0.763, 1.519)
		Healthy	56			
	AUC(INF) (ng ^h /mL)	Impaired	216	Impaired/Healthy	1.097	(0.828, 1.453)
		Healthy	197			
AUC(0-T) (ng ^h /mL)	Impaired	210	Impaired/Healthy	1.097	(0.831, 1.448)	
	Healthy	192				
B (Moderate)	C _{max} (ng/mL)	Impaired	77	Impaired/Healthy	1.016	(0.720, 1.432)
		Healthy	76			
	AUC(INF) (ng ^h /mL)	Impaired	286	Impaired/Healthy	1.383	(1.044, 1.832)
		Healthy	207			
	AUC(0-T) (ng ^h /mL)	Impaired	278	Impaired/Healthy	1.381	(1.046, 1.823)
		Healthy	201			
C (Severe)	C _{max} (ng/mL)	Impaired	50	Impaired/Healthy	0.941	(0.667, 1.328)
		Healthy	54			
	AUC(INF) (ng ^h /mL)	Impaired	338	Impaired/Healthy	1.767	(1.334, 2.341)
		Healthy	191			
	AUC(0-T) (ng ^h /mL)	Impaired	319	Impaired/Healthy	1.718	(1.301, 2.268)
		Healthy	186			

For BMS-510849, in general, all the PK parameters for hepatic impaired subjects were decreased compared to healthy subjects, in all the hepatic function groups (Table 15).

Table 15: Summary statistics for BMS-510849 PK parameters by hepatic function group and subject status

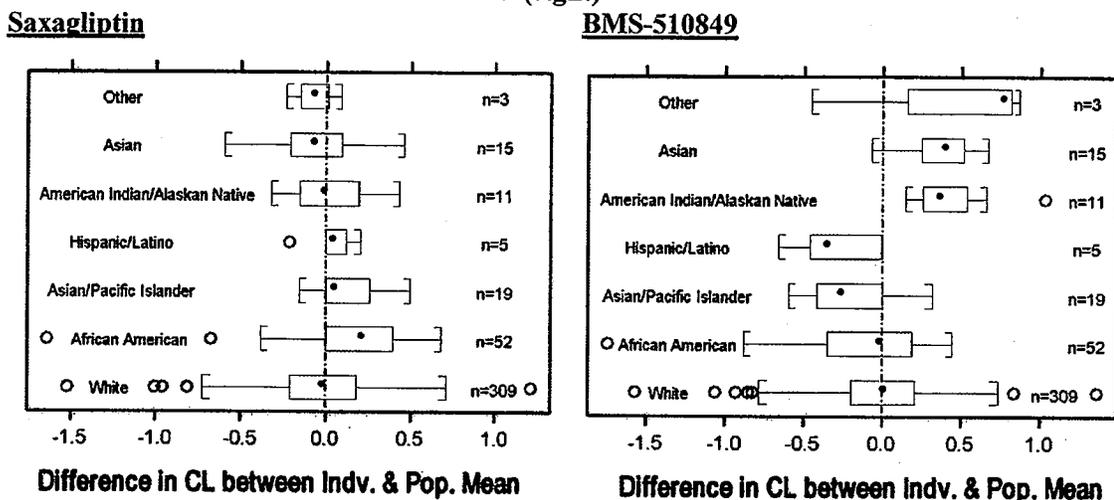
Hepatic Function Group	Subject Status	BMS-510849 Pharmacokinetic Parameters				
		C _{max} (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng ² h/mL) Geom. Mean (CV%)	AUC(0-T) (ng ² h/mL) Geom. Mean (CV%)	T _{max} (h) Median (Min, Max)	T _{1/2} (h) Mean (SD)
A (Mild)	Impaired (n = 6)	84.7 (31)	472 (29)	459 (29)	1.50 (1.00, 3.00)	3.52 (0.57)
	Healthy (n = 6)	103.4 (28)	602 (11)	578 (12)	1.50 (1.50, 3.00)	4.17 (1.34)
B (Moderate)	Impaired (n = 6)	94.1 (31)	500 (42)	482 (43)	1.75 (1.00, 2.00)	4.03 (1.13)
	Healthy (n = 6)	111.6 (23)	540 (27)	522 (28)	1.00 (1.00, 2.50)	3.53 (0.90)
C (Severe)	Impaired (n = 6)	55.3 (23)	335 (69)	310 (71)	2.25 (1.00, 3.00)	5.71 (2.58)
	Healthy (n = 6)	86.2 (33)	560 (28)	484 (28)	1.50 (1.00, 2.50)	3.53 (0.48)

Reviewer's comments

- Saxagliptin is predominantly metabolized in the liver by CYP3A and the exposure is expected to increase in hepatic impairment.
- Compared to matched healthy subjects, there was a trend towards higher exposure for saxagliptin and lower exposure for BMS-510849 with increasing severity of hepatic impairment, indicating a reduced capacity to metabolize saxagliptin as hepatic function declines.
- There was no correlation with smoking status.
- Sponsor's conclusions regarding no dosage adjustments based on hepatic function is acceptable.
- Race

In the population pharmacokinetic analysis, saxagliptin clearance was plotted against the change in clearance from the population mean. Figure 25, left panel indicates for saxagliptin that clearance is unchanged across different races. While, right Panel indicates that the metabolite clearance for some of these different race groups is increased (Asian or American Indian/Alaskan Natives) or decreased (Hispanic/Latino) clearance. However, these changes are insufficient to recommend a labeling adjustment, particularly since they occur on the clearance of the active metabolite which is half as potent as saxagliptin.

Figure 25: Effect of race on the pharmacokinetics of saxagliptin (left) and BMS-510849 (right)



2.3.2 *What pharmacogenetics information is there in the application and is it important or not?*

Pharmacogenetics/pharmacogenomic information is not available in this submission. However, the sponsor has collected blood samples in most of the Clinical Pharmacology studies in order to conduct exploratory pharmacogenomic analyses if needed in the future.

2.3.3 *What pregnancy and lactation use information is there in the application?*

Saxagliptin was not administered to pregnant and lactating women in clinical studies and is not recommended in pregnant women. Preclinical data addressing the teratogenic potential indicates that saxagliptin is not teratogenic in animals. Please refer to pharmacology/toxicology review by Dr. Fred Alavi for detailed assessment of preclinical teratogenic effects of saxagliptin. It is not known if saxagliptin is excreted in human milk and is not indicated to be given to nursing mothers.

2.3.4 *What pediatric use information is there in the application?*

The sponsor's pediatric plan was presented to the PeRC on March 11, 2009. The sponsor has stated in the pediatric plan that simulations of saxagliptin and BMS-510849 exposures over a 30- to 90-kg weight range following a 5-mg oral dose of saxagliptin indicated that body masses ≥ 50 kg did not markedly affect the systemic exposure to saxagliptin and BMS-510849. Sponsor is predicting that the systemic exposure of saxagliptin and BMS-510849 will be similar between pediatric patients with body weight greater than or equal to 50 kg and adults following an oral 5-mg dose of saxagliptin. According to the sponsor, systemic exposure to saxagliptin and BMS-510849 is predicted

to be higher in pediatric patients with body weight of 30 kg to <50 kg than in adults following an oral 5-mg dose of saxagliptin. Therefore, a body weight-based dosage regimen is proposed: pediatric patients with body weight ≥ 50 kg will receive the usual adult 5-mg oral QD dose of saxagliptin, and pediatric patients with body weight 30 kg to <50 kg will receive a 2.5-mg oral QD dose of saxagliptin. The proposed pediatric study will exclude patients with body weight less than 30 kg.

The sponsor is proposing to investigate the safety, tolerability and efficacy of saxagliptin monotherapy versus placebo, and provide a reference comparison to the safety, tolerability and efficacy of metformin, for the treatment of type 2 diabetes in pediatric patients aged 10 to < 18 years. Saxagliptin therapy is being planned to be administered by body weight category. In addition to the main study mentioned above, a non-randomized, open-label, combination treatment arm will be included in which saxagliptin will be assigned by body weight as add on combination for metformin to patients who are previously on metformin therapy or with a HbA1c of 8.5% or higher. The pharmacokinetic sub-study will be implemented at the beginning of the 2-week run-in period, prior to randomization and treatment in the double blind main study arms, and prior to active treatment in the open-label, non-randomized study arm. The pharmacokinetics of saxagliptin will be evaluated based on a sub-study in which a single dose of 2.5 mg or 5 mg saxagliptin will be administered to patients in each of the 2 weight categories. A minimum of 12 total patients (6 from each of 2 weight categories) and a maximum of 24 patients (12 from each of 2 weight categories) who have consented to participate in the pharmacokinetic portion of the study are being planned be enrolled.

PeRC agreed with the overall approach but recommended that the sponsor incorporate dose-finding in pediatric patients

2.4 Extrinsic Factors

2.4.1 *Is the drug a substrate of CYP enzymes?*

Yes. Saxagliptin is a substrate of CYP enzymes. The major metabolite of saxagliptin in all species and was identified as BMS-510849, a mono-hydroxylated derivative of BMS-477118. CYP3A4 and CYP3A5 were the major human CYP isoforms involved in the metabolism of BMS-477118. When saxagliptin was incubated with HLM in the presence of ketoconazole (1 μ M), a inhibitor of CYP3A4/5, or troleandomycin (20 μ M), a time-dependent inhibitor of CYP3A4/5, the formation of BMS-510849 was inhibited by >97%. There was no inhibition with inhibitors of other CYP enzymes indicating that saxagliptin is a substrate of CYP3A4/5. Other enzymes involved to a very minor extent include CYP1A2, 2C19 and 2D6.

2.4.2 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Inhibition: Incubation of saxagliptin (0.1 to 50 μM) and BMS-510849 ($\leq 200 \mu\text{M}$) in human hepatic microsomal suspensions resulted in no concentration dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. Additionally, there was no time-dependent (mechanism based) inhibition of any of the CYP enzymes.

Induction: At the concentrations tested (0.2-25 μM), exposure of human hepatocytes to saxagliptin does not appear to be associated with significant induction of cytochrome P450 1A2, 2B6 or 3A4 mRNA expression or enzyme activity *in vitro*. Consistent conclusion cannot be drawn with regard to induction of CYP2C9, since there was increase in mRNA levels but was not correlated with corresponding increase in CYP2C9 activity in all 3 hepatocyte preparations from 3 donors. Similar results were obtained with BMS-510849. Of the 3 hepatocyte preparations, preparation from one donor, (Hu211) showed induction of CYP2C9 mRNA in response to both saxagliptin and BMS-510849.

2.4.3 *Is the drug a substrate and/or an inhibitor/inducer of P-glycoprotein transport processes?*

Saxagliptin appears to be a substrate of P-glycoprotein. Saxagliptin was subject to efflux with polarization ratios in 22L1 (P-glycoprotein expressing) cells approximately 3-fold higher than in CLD (control) cells as compared to efflux ratio of over 9-fold with digoxin. On the other hand, BMS-510849 does not appear to be a substrate of P-glycoprotein, the polarization ratio was only 0.8-1.1 when compared to control cells. P-glycoprotein photoaffinity study indicated that saxagliptin bound to P-glycoprotein only at high concentration tested (50 μM). Saxagliptin's ability to inhibit P-glycoprotein as well as the effect of P-glycoprotein inhibitor on saxagliptin transport was not investigated *in vitro*. However, based on *in vivo* DDI study with digoxin, saxagliptin does not appear to inhibit or induce P-glycoprotein. Additionally, the sponsor has addressed the effect of P-glycoprotein inhibition using diltiazem, which is a P-glycoprotein inhibitor as well as moderate CYP3A4 inhibitor (see 2.4.5).

2.4.4 *Are there other metabolic/transporter pathways that may be important?*

The renal clearance of saxagliptin in humans is determined to be approximately 230 mL/min (approximately twice that of the glomerular filtration rate of 120 mL/min. These values indicate that saxagliptin excretion via the renal route is a combination of passive glomerular filtration and active tubular secretion.

The transport of saxagliptin and BMS-510849 was examined *in vitro* employing transfected cells (HEK-293 or MDCK) and *Xenopus laevis* oocytes expressing one of the following human uptake transporters, *viz.* OATP1B1 (OATP-C), OATP1B3 (OATP8),

OCT1, OCT2, OAT1, OAT3, PEPT1, and PEPT2. The results show that both saxagliptin and its active metabolite (BMS-510849) are not substrates of these transporters *in vitro*.

Thus, although saxagliptin was not a substrate for any of these transporters, there is a possibility of involvement of as yet unknown transporters in the kidney.

2.4.5 What are the drug-drug interactions?

Drug interaction was evaluated as follows and the results are summarized in Table 16, 17 and 18:

- DDI between saxagliptin and other drugs: glyburide, pioglitazone, metformin, digoxin and simvastatin.
- Effect of other drugs on saxagliptin exposure: maalox Max, famotidine, and omeprazole
- The effect of metabolic modulators on saxagliptin exposure: ketoconazole, diltiazem and rifampin

Saxagliptin caused about 16% and 14% increase in the C_{max} of glyburide and pioglitazone respectively and about 12% decrease in the simvastatin C_{max}. There was 16% increase in the simvastatin acid AUC in presence of saxagliptin (Table 16). In addition, there was a statistical decrease in C_{max} of saxagliptin presence of Maalox max (26% ↓) and metformin (21% ↓) (Table 17). The 90% CI for these fell outside of the 80-125% limit for C_{max} in presence of these drugs with no impact on the AUC of saxagliptin. These changes are not likely to be clinically significant. As shown in Table 18, the most significant changes in the saxagliptin exposure occurred in presence of metabolic modulators.

Table 16: Effect of saxagliptin on other drugs

Saxagliptin Regimen	Substrate	GMR (90% CI)	
		AUC	C _{max}
Saxagliptin 10 mg	Glyburide 5mg (2C9)	1.06 (1.00 – 1.13)	1.16 (1.06 – 1.28)
Saxagliptin 100 mg	Metformin 1000 mg (OCT 1 & 2)	1.20 (1.17 – 1.24)	1.09 (1.01 – 1.19)
Saxagliptin 10 mg QD (Days 1-3) and then (Days 9-13)	Pioglitazone 45 mg (Days 4-13)	1.08 (0.99 – 1.17)	1.14 (1.03 – 1.27)
Saxagliptin 10 mg QD (Days 1-4) and (Days 9-12)	Simvastatin 40 mg (3A4) (Days 5-12)	1.04 (0.94 – 1.15)	0.88 (0.74 – 1.06)
	Simvastatin acid	1.16 (1.04 – 1.29)	1.00 (0.89 – 1.13)
Saxagliptin 10 mg (Day 1-7)	Digoxin: (P-glycoprotein) (Day 1, 0.25 mg q6h; Day 2, 0.25 mg q 12h; Days 3-7 0.25 mg QD)	1.06 (1.02 – 1.11)	1.09 (1.00 – 1.19)

Bolded values indicate out of BE criteria.

Table 17: Effect of other drugs on saxagliptin

Drug	Effect on saxagliptin & BMS-510849	GMR (90% CI)	
		AUC	Cmax
Glyburide 5 mg	Saxagliptin 10 mg	0.98 (0.95 - 1.01)	1.08 (1.02 - 1.14)
Maalox max 30 mL prior to saxagliptin	Saxagliptin 10 mg	0.95 (0.91 - 0.99)	0.74 (0.65 - 0.84)
Famotidine 40 mg (OCT inhibitor) given 3 h prior to saxagliptin	Saxagliptin 10 mg	1.02 (0.98 - 1.07)	1.13 (0.99 - 1.29)
Omeprazole 40 mg (P-glycoprotein substrate) QD (Days 1-4) prior to saxagliptin	Saxagliptin 10 mg	1.12 (1.08 - 1.17)	0.97 (0.85 - 1.11)
Metformin 1000 mg	Saxagliptin 100 mg	0.98 (0.92 - 1.04)	0.79 (0.71 - 0.87)
	BMS-510849	0.99 (0.95 - 1.02)	0.88 (0.82 - 0.94)
Pioglitazone 45 mg (Days 4-13)	Saxagliptin 10 mg QD (Days 1-3) and then (Days 9-13)	1.11 (1.06 - 1.16)	1.11 (1.03 - 1.20)
Simvastatin 40 mg (Days 5-12)	Saxagliptin 10 mg QD (Days 1-4) and (Days 9-12)	1.12 (1.09 - 1.15)	1.21 (1.11 - 1.31)
	BMS-510849	1.02 (0.99 - 1.05)	1.08 (1.02 - 1.14)
Digoxin (Day 1, 0.25 mg q6h; Day 2, 0.25 mg q 12h; Days 3-7 0.25 mg QD)	Saxagliptin 10 mg (Day 1-7)	1.05 (0.99 - 1.11)	0.99 (0.87 - 1.12)
	BMS-510849	1.06 (1.01 - 1.12)	1.02 (0.91 - 1.14)

Bolded values indicate out of BE criteria.

Table 18: Effect of metabolic modulators on saxagliptin

Inhibitor/Inducer	Substrate	GMR (90% CI)	
		AUC	Cmax
Ketoconazole 200 mg q12 h for 6 days (3A4)	Saxagliptin 100 mg	2.48 (2.33 - 2.65)	1.62 (1.47 - 1.80)
	BMS-510849	0.09 (0.07 - 0.11)	0.05 (0.05 - 0.06)
	Ketoconazole	0.87 (0.79 - 0.95)	0.84 (0.77 - 0.92)
Ketoconazole 200 mg q12 h for 6 days (3A4)	Saxagliptin 20 mg	3.79 (3.39 - 4.24)	2.44 (2.03 - 2.93)
Diltiazem (3A4) 360 mg (Days 2-9)	Saxagliptin 10 mg (Day 1 and Day 9)	2.13 (1.99 - 2.28)	1.63 (1.40 - 1.89)
	BMS-510849	0.64 (0.59 - 0.69)	0.56 (0.49 - 0.64)
	Diltiazem	1.10 (0.97 - 1.25)	1.16 (0.98 - 1.36)
Rifampin 600 mg QD (Days 2-7)	Saxagliptin 5 mg QD (Days 1, and 7)	0.20 (0.17 - 0.25)	0.47 (0.38 - 0.57)
	BMS-510849	1.04 (0.98 - 1.11)	1.39 (1.23 - 1.56)

Bolded values indicate out of BE criteria.

Reviewer's comments:

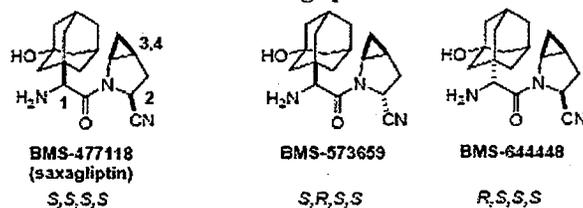
- *DDI with strong CYP3A4/5 inhibitors:* The proposed clinical dose for saxagliptin is 5 mg. The sponsor used a very high dose (100 mg) of the substrate (saxagliptin) in the DDI study. There was about 2.5 fold increase in AUC in presence of ketoconazole. 14 of 15 subjects experienced a decline in lymphocyte count on Day 10 following co-administration saxagliptin and ketoconazole. This was also accompanied with pyrexia and chills. In order to characterize this adverse event, another PD study was conducted and the effect of co-administration was determined. In this case, the sponsor used 20 mg saxagliptin with ketoconazole and there was a 3.8 fold increase in AUC. In presence of diltiazem (moderate inhibitor) there was a 2.1 fold increase in AUC of saxagliptin (10 mg). Since the sponsor did not use the lowest possible dose of the substrate in the ketoconazole DDI study, the extent of increase in exposure of saxagliptin is unknown. In addition, considering the increase in exposure of saxagliptin and the adverse events that resulted in presence of ketoconazole, it is recommended to reduce the dose to 2.5 mg when patients will be prescribed strong CYP3A4/5 inhibitors.
- *DDI with CYP3A4/5 inducers:* There was significant induction of CYP3A4/5 with 80% decrease in saxagliptin exposure. Although this was not associated with corresponding increase in metabolite exposure, there was about 40% increase in BMS-510849 C_{max}. Induction also resulted in a decrease in saxagliptin half life from 3.02 to 1.7 h. This metabolic induction is also evident in a 5-fold increase in the metabolite-to-parent AUC ratio. The mean DPP4 inhibition for the trough sample (24 h post dose with saxagliptin) was around 13% lower when saxagliptin was co-administered with rifampin relative to saxagliptin alone. The sponsor evaluated the total active moiety exposure with and without rifampin and determined that there was about 25% decrease in the total active moiety exposure in presence of rifampin. The clinical significance of these changes is unknown. However, no dosage adjustment is needed when co-administered with strong inducers of CYP3A4/5.
- Sponsor did not conduct DDI study with warfarin.
- Sponsor has been requested to submit the report of DDI study with oral contraceptives once the study is completed.

2.4.6 *Are there any other questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

Saxagliptin is a chiral molecule with four stereogenic centers (*S,S,S,S* configuration), two being fixed in relative stereochemistry as part of the cyclopropane ring. Therefore, eight diastereomeric structures are theoretically possible. The sponsor did not address the chiral inversion and this was communicated in the filing letter. The sponsor responded to **Agency's request and reanalyzed the samples** from ADME study. The human plasma and urine samples from human ADME study were then re-examined for the presence of radioactivity or MS signal at the retention times corresponding to the authentic standards. There was no evidence for any signal, thus it was concluded that these components were not present in these human samples. To further investigate the potential for formation of

diastereomers of saxagliptin (BMS-573659 and BMS-644448) under biological conditions were examined with the validated LC-MS assay used for saxagliptin quantitation in conjunction with late stage clinical trials. As above, the mass spectral chromatograms of the clinical study samples were examined for the presence of a peak corresponding to the standards, but no signals were detected at the retention times of BMS-573659 and BMS-644448.

Figure 26: Structure of saxagliptin and diastereomers



2.5 General Biopharmaceutics

2.5.1 *Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?*

Saxagliptin can be considered as BCS class 3 drug (high solubility, low permeability).

Solubility: The aqueous solubility of saxagliptin is pH dependent (24 ± 3 °C), increasing from 103.5 mg/mL at pH 0.7, to 149.2 mg/mL at pH 5.9, then decreasing to 46.9 mg/mL at pH 6.94 and 17.8 mg/mL at pH 8.5. Since the solubility in all pHs is greater than 0.02 mg/mL (highest tablet strength, 5 mg in 250 mL), saxagliptin can be considered *highly soluble* based on the BCS guidance.

Permeability: Saxagliptin was poorly permeable in the Caco-2 transcellular permeability assay (permeability coefficient (Pc) values of 18 to 20 nm/sec) and in the Parallel Artificial Membrane Permeability Assay (PAMPA) intrinsic permeability assay (mean Pc: 4 to 59 nm/sec). In these assays, saxagliptin flux was comparable to control compounds that exhibit poor absorption in humans. In ADME mass balance study, the total radioactivity recovered in urine was ~75%. There was about 22% of the radioactivity recovered in feces which was mainly due to oxidative metabolites. This indicates that saxagliptin is extensively metabolized, however the GI stability as well as the discrepancy between *in vivo* and *in vitro* data needs to be addressed in order to characterize as *highly permeable* drug.

Dissolution. Please refer to ONDQA review for details.

2.5.2 *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?*

The clinical tablet formulations used in the Phase 3 program differ from the proposed commercial tablet formulations in color and imprinting. At the pre-NDA meeting, the sponsor stated that the Phase 3 formulation and the to-be-marketed formulation were equivalent by SUPAC Guidelines. The Division agreed with the sponsor regarding this issue (meeting minutes, dated 12/14/07). Therefore, there are no pivotal bioequivalence or dose strength equivalence studies in the saxagliptin development program.

For the initial clinical studies drug substance in (), was employed in the clinical development program. Subsequently, drug substance, as the () monohydrate (designated as ()), was selected for further development. The approach selected for the tablets involves

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Relative bioavailability of the tablet formulation was compared to that of the capsule formulation (Study 037, reviewed by Dr. Zdrojewski) used in early Phase 1 trials. The 5 mg tablet formulation met the bioequivalence criteria for the AUC_{inf} and AUC_{0-t} when compared to the 5 mg capsule. The 90% confidence interval for C_{max} was outside of the prespecified interval of 80-125%. The C_{max} resulting from the tablet was ~10% higher as compared to that from capsule formulation.

2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The results suggest that there was an effect of a high-fat meal on saxagliptin AUC_{inf} (Figure 27). When administered with a high-fat meal, saxagliptin AUC_{inf} increased by 27%. Although C_{max} increased by 7.7% in presence of food, the 90% confidence intervals for ratios of C_{max} geometric means fell within the equivalence interval of 80% to 125% (Table 19). The T_{max} was also delayed in presence of food (median T_{max} of 0.99 h with meal as compared to 0.53 h).

Figure 27: Mean (+ SD) plasma concentration-time profiles for saxagliptin following administration of single oral 10 mg dose of saxagliptin to healthy subjects in the fasted state and after a high-fat meal (n=14)

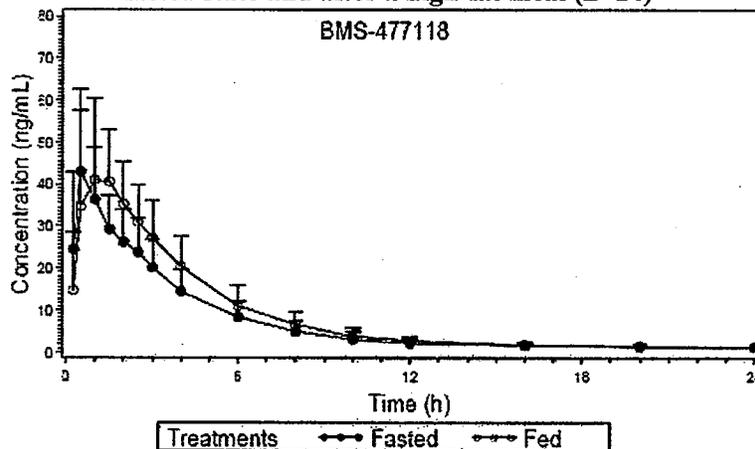


Table 19: Summary statistics for saxagliptin pharmacokinetic parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		B/A Ratio of Adjusted Geometric Means	
	A	B	Point Estimate	90% CI
C _{max} (ng/mL)	46.40	49.97	1.077	(0.930, 1.246)
AUC(INF) (ng·h/mL)	150.11	190.69	1.270	(1.188, 1.358)

A = 10 mg saxagliptin in fasted conditions

B = 10 mg saxagliptin following a high-fat meal

On the other hand, there was no change in the exposure of BMS-510849 when saxagliptin was administered with food, however the C_{max} decreased by 18%.

Reviewer's Comments:

- This study was conducted with the highest dose (10 mg) that was used in Phase 3 program.
- The formulation used was a () tablet which is almost identical to the anticipated marketed formulation. This was discussed at the Pre-NDA meeting with the Agency and it was agreed that the final to-be-marketed formulation was not significantly different to that of the formulation used in the definitive food effect study.
- Sponsor is proposing that saxagliptin can be administered either in fasted or fed state. Although there was about 27% increase in saxagliptin exposure with meal, this is not clinically significant. The T_{max} was also delayed in presence of food (median T_{max} of 0.99 h with meal as compared to 0.53 h). The sponsor's dosing administration approach is acceptable.
- **Biowaiver request:** The sponsor is requesting biowaiver for conducting additional clinical food effect studies with the proposed to-be-marketed 2.5 mg and 5 mg tablets and to apply the findings from the 10 mg food effect study to

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these lower strength tablets. No separate clinical study is required to characterize the effect of food on the lower strength formulations based on:

- Similarity of composition of 2.5 mg, 5 mg and 10 mg tablets.
- Linearity in saxagliptin PK in this dose range.
- Saxagliptin can be considered as highly soluble based on the 5 mg tablet strength (and also 10 mg tablet strength).
- Dissolution profiles of all 3 strengths is rapid and similar in 3 pH (0.1N HCl, 4.5 and 6.8)
- Therefore, biowaiver can be granted.

2.6 Analytical Section (reviewed by Dr. Zdrojewski)

2.6.1 *What bioanalytical methods are used to assess concentrations?*

The active moieties (saxagliptin and BMS-510849) were measured in human k_3 EDTA plasma using liquid chromatography/tandem mass spectrometry, after online extraction and turboionspray ionization.

The extraction method was later changed to an offline extraction and the chromatography was enhanced to detect other mono-hydroxylated metabolites with the same mass spectral characteristics as BMS-510849. Evaluation of the quantification differences due to the interference resulted in changes of 8.7 and 5.8% difference in C_{max} and AUC_{inf} respectively for parameters assessed in plasma and 12.5% for the amount excreted in urine.

2.6.2 *Which metabolites have been selected for analysis and why?*

BMS-510849 was analyzed in clinical studies. BMS-510849 is a mono-hydroxylated product and the major metabolite of saxagliptin.

2.6.3 *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total plasma concentration was measured for all moieties.

2.6.4 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The ranges for the calibration curve in plasma were 5.00 – 1000 ng/mL and 10-2000 ng/mL for saxagliptin and BMS-510849 respectively. While the ranges for the calibration curve in urine were 25-5000 ng/mL and 50-10000 ng/mL for saxagliptin and BMS-510849 respectively. All calibration curves were fitted to a 1/x weighted quadratic regression model. Clinical study concentrations were within the calibration range. Some

samples were above ULOQ, but dilution of samples was also evaluated during the validation.

2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ in plasma are 5.00 ng/mL and 10.0 ng/mL for saxagliptin and BMS-510849 respectively. The ULOQ in plasma are 1000 ng/mL and 2000 ng/mL for saxagliptin and BMS-510849 respectively.

2.6.6 What are the accuracy, precision, and selectivity at these limits?

For both laboratories, accuracy was within $\pm 8.8\%$ and $\pm 11.8\%$ for determination of saxagliptin and BMS-510849 in plasma and urine, respectively.

2.6.7 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Samples containing saxagliptin and BMS-510849 were stable for 24h at room temperature and for 2 weeks at -20°C for short term storage. Freeze thaw stability over three cycles was shown for both analytes. Processed samples were stable for at least 80 h at room temperature.

2.6.8 What is the QC sample plan?

The following QCs were used in both the labs - 15.0, 400, 800, 10000 ng/mL for saxagliptin and 30.0, 800, 1600, 20000 ng/mL for BMS-510849, () used the LLOQ as QC for both analytes for analysis of drug and metabolite in plasma. For analysis in urine the following QC's were used at Bristol-Myers Squibb 75.0, 2000, 4000, 5000 ng/mL for saxagliptin and 150, 4000, 8000, 10000 ng/mL for BMS-510849. () used 25.0, 75.0, 2000, 4000, 25000 ng/mL for saxagliptin and 50.0, 150, 4000, 8000, 50000 ng/mL as QC's for BMS-510849 quantification in urine.

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

4.2 Individual Study Reviews:

DDI studies:

Effect of metabolic modulators (rifampicin, diltiazem and ketoconazole) on saxagliptin exposure

Effect of other drugs (maalox Max, famotidine, omeprazole)

DDI between saxagliptin on other drugs (glyburide, pioglitazone, metformin, digoxin, simvastatin)

Clinical Study CV181026: Pharmacokinetic drug interaction study with saxagliptin and glyburide in healthy subjects (Aug-Oct, 2005)

The main objectives were to determine the effect of glyburide on the pharmacokinetics of saxagliptin in healthy subjects and to determine the effect of saxagliptin on the PK of glyburide in healthy subjects.

This was an open-label, randomized, three-period, three-treatment, crossover study balanced for carryover effects in healthy subjects. Each subject received the following three treatments following a fast of at least 8 hours according to the randomization schedule: single oral dose of 10 mg saxagliptin tablet (Treatment A), single oral dose of 5 mg glyburide (Micronase®) tablet (Treatment B) and co-administration of single oral doses of 10 mg saxagliptin tablet + 5 mg glyburide tablet (Treatment C). The results are summarized in the following tables.

Summary statistics for saxagliptin PK parameters

Pharmacokinetic Parameter	Treatment	
	A (n=30)	C (n=30)
C _{max} (ng/mL)		
Geometric Mean (C.V. %)	26 (22)	28 (28)
AUC(INF) (ng·h/mL)		
Geometric Mean (C.V. %)	169 (21)	165 (22)
AUC(0-T) (ng·h/mL)		
Geometric Mean (C.V. %)	160 (22)	156 (23)
T _{max} (h)		
Median (Min, Max)	1.50 (0.50, 3.00)	1.50 (0.50, 2.00)
T-HALF (h)		
Mean (S.D.)	2.87 (0.55)	2.63 (0.37)

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (C/A)	
	A	C	Point Estimate	90% C.I.
C _{max} (ng/mL)	26	28	1.08	(1.02, 1.14)
AUC(INF) (ng·h/mL)	169	165	0.98	(0.95, 1.01)

Summary statistics for BMS-510849 PK parameters

Pharmacokinetic Parameter	Treatment	
	A (n=30)	C (n=30)
C _{max} (µg/mL) Geometric Mean (C.V. %)	62 (19)	65 (20)
AUC _(0-∞) (µg·h/mL) Geometric Mean (C.V. %)	468 (21)	488 (21)
AUC ₍₀₋₁₎ (µg·h/mL) Geometric Mean (C.V. %)	471 (22)	472 (21)
T _{max} (h) Median (Min, Max)	3.00 (1.50, 4.00)	3.00 (1.00, 4.00)
T- _{1/2} (h) Mean (S.D.)	3.55 (0.47)	3.43 (0.42)

Summary statistics for glyburide PK parameters

Pharmacokinetic Parameter	Treatment	
	B (n=30)	C (n=30)
C _{max} (µg/mL) Geometric Mean (C.V. %)	103 (3.7)	120 (31)
AUC _(0-∞) (µg·h/mL) Geometric Mean (C.V. %)	881 (3.6)	933 (44)
AUC ₍₀₋₁₎ (µg·h/mL) Geometric Mean (C.V. %)	847 (3.8)	910 (45)
T _{max} (h) Median (Min, Max)	3.00 (3.00, 18.00)	8.00 (2.00, 18.00)
T- _{1/2} (h) Mean (S.D.)	7.76 (5.57)	4.84 (2.94)

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (C/B)	
	B	C	Point Estimate	90% C.I.
C _{max} (µg/mL)	103	120	1.16	(1.06, 1.28)
AUC _(0-∞) (µg·h/mL)	881	933	1.06	(1.00, 1.13)

Comments:

- Glyburide, a sulfonylurea is widely used as an oral anti-hyperglycemic treatment for type 2 diabetes mellitus. Saxagliptin is likely to be used in combination with glyburide. This study assessed the potential for PK interaction between these two agents.
- A 10 mg dose of saxagliptin is the highest dose that was studied in the Phase 3 clinical program and 5 mg of glyburide is the highest recommended starting dose in drug naive individuals.

- The terminal half-lives of saxagliptin and glyburide are 2.5 and 10 hours, respectively. The washout period of at least 5 days between each dose is acceptable.
- There was no effect of glyburide on the AUC_{inf} and C_{max} of saxagliptin. The pharmacokinetics of BMS-510849 appeared similar when 10 mg saxagliptin was administered with or without 5 mg glyburide.
- Glyburide is considered to be a useful and sensitive probe drug for human CYP2C9 activity. The results of this study will provide evidence for saxagliptin's effect or lack of effect on CYP2C9 activity. The geometric means for C_{max} and AUC(INF) of glyburide increased by 16% and 6%, respectively, relative to those observed following administration of 5 mg glyburide alone. The 90% confidence interval for the ratios of population geometric means, with and without saxagliptin, were within the (80%, 125%) no-effect interval for AUC(INF) of glyburide but not for its C_{max}. Hypoglycemia was AE of clinical interest and was more following co-administration of glyburide and saxagliptin (3 subjects) as compared to single glyburide administration (1 subject).
- The half-life values of glyburide when administered alone and co-administered with saxagliptin were 7.76 and 4.84 hrs, respectively. The larger half-life for glyburide administered alone was driven by 5 subjects who had half-life values of greater than 14 hours. However, the portion of the AUC accounted for from the last quantifiable plasma concentration extrapolated to infinity in these subjects was less than 10% of the total AUC value.

Clinical Study CV181053: Effect of diltiazem on the single-dose pharmacokinetics of saxagliptin in healthy subjects (Feb-Sep 2007)

Since hypertension commonly coexists with type 2 diabetes, saxagliptin is anticipated to be co-administered with diltiazem (Cardizem® LA) in some patients. The main objective was to assess the effects of diltiazem on the pharmacokinetics of single-dose saxagliptin in healthy subjects.

This was an open-label, non-randomized, sequential study in healthy subjects. 12 Subjects received all of the following 3 treatments (Table). Two (2) subjects (CV181053-1-3 and CV181053-1-14) discontinued due to AEs during Treatment B. Saxagliptin was administered following a fast of at least 10 hours. Subjects were maintained in a fasted state for 4 h postdose of saxagliptin.

Treatment (Day)	Total Daily Dose of Saxagliptin	Total Daily Dose of Diltiazem (Cardizem® LA)
A (Day 1)	Single 10 mg tablet	-
B (Days 2-8)	-	360 mg tablet
C (Day 9)	Single 10 mg tablet	360 mg tablet
C (Day 10)	-	360 mg tablet

As shown above, a single dose of 10 mg saxagliptin was administered following a fast of at least 10 hours (h) on Day 1 (Treatment A). On Days 2 through 8, subjects received once-daily oral doses of 360 mg diltiazem administered as Cardizem® LA (Treatment B). On Day 9, subjects received a single oral dose of 10 mg saxagliptin along with the dose of 360 mg diltiazem (Treatment C). A single dose of 360 mg diltiazem was administered alone on Day 10 (Treatment C).

When saxagliptin 10 mg was co-administered with diltiazem 360 mg, the geometric mean for C_{max}, AUC(INF) and AUC(0-T) of saxagliptin increased by 63.1%, 109.4% and 113.3%, respectively, relative to those observed following administration of saxagliptin 10 mg alone. The 90% confidence intervals for the ratios of population geometric means, with and without diltiazem, were all entirely above the (80%, 125%) no-effect interval described in the Guidance on drug interaction studies.

Table: Summary statistics for saxagliptin PK parameters

Pharmacokinetic Parameter	Treatment	
	Treatment A (n = 12)	Treatment C (n = 12)
C _{max} (ng/mL) Geometric Mean (CV%)	53 (40)	87 (33)
AUC(INF) (ng·h/mL) Geometric Mean (CV%)	158 (25)	332 (27)
AUC(0-T) (ng·h/mL) Geometric Mean (CV%)	152 (26)	325 (27)
T _{max} (h) Median (Min, Max)	0.50 (0.50, 2.00)	0.50 (0.25, 1.00)
T-1/2 (h) Mean (SD)	2.38 (0.31)	3.30 (0.46)

Treatments: A = 10 mg saxagliptin administered alone

C = 10 mg saxagliptin administered with 360 mg diltiazem LA

Pharmacokinetic Parameter	Geometric Means		Ratios of Geometric Means (Trt C / Trt A) Point Estimate (90% CI)
	Treatment A (n = 12)	Treatment C (n = 12)	
C _{max} (ng/mL)	53	87	1.631 (1.400, 1.899)
AUC(INF) (ng·h/mL)	158	332	2.094 (1.967, 2.229)
AUC(0-T) (ng·h/mL)	152	325	2.133 (1.998, 2.278)

Simultaneously, when saxagliptin 10 mg was co-administered with diltiazem 360 mg, the geometric mean for C_{max}, AUC(INF) and AUC(0-T) of the metabolite, BMS-510849 decreased by 43.5%, 34.3% and 35.6%, respectively, relative to those observed following administration of saxagliptin 10 mg alone. The 90% confidence intervals for the ratios of population geometric means, with and without diltiazem, were all entirely below the limit of 80-125%.

Table: Summary statistics for bms-510849 PK parameters

Pharmacokinetic Parameter	Treatment	
	Treatment A (n = 12)	Treatment C (n = 12)
C _{max} (ng/mL) Geometric Mean (CV%)	111 (20)	63 (26)
AUC(INF) (ng·h/mL) Geometric Mean (CV%)	538 (25)	353 (23)
AUC(0-T) (ng·h/mL) Geometric Mean (CV%)	526 (25)	338 (24)
T _{max} (h) Median (Min, Max)	1.50 (1.00, 2.00)	1.50 (1.00, 2.50)
T-HALF (h) Mean (SD)	3.04 (0.58)	3.30 (0.53)

Comments:

- Since diltiazem is a moderate CYP3A4/5 inhibitor, this study evaluated the potential interaction between saxagliptin and diltiazem at a dose of 360 mg, once-daily in healthy subjects, a dose higher than the commonly prescribed dose in clinical practice.
- A DDI was observed in this study due to CYP3A4/5 inhibition. The exposure increased for the parent drug (~2.1 fold), with an increase in half-life from 2.38 to 3.3 h.
- Based upon plasma concentrations of diltiazem for samples collected prior to diltiazem dose on Days 6, 7 and 8, a steady state level for diltiazem plasma concentrations had been achieved prior to co-administration of saxagliptin with diltiazem on Day 9.
- Co-administration of saxagliptin did not affect overall diltiazem exposure (ie, the 90% CI for the geometric mean AUC(TAU) ratio was wholly contained within the 80%-125% no-effect interval). Although C_{max} did not meet the criteria, the observed 16% increase in geometric mean C_{max} of diltiazem is not likely to be clinically meaningful.

Clinical Study CV181035: Effect of maalox max®, effect of famotidine, or effect of omeprazole on the pharmacokinetics of saxagliptin in healthy subjects. (May-Jun 2006)

Maalox Max® (active ingredients: magnesium hydroxide 400 mg/5 mL, aluminum hydroxide 400 mg/5 mL, and simethicone 40 mg/5 mL) is an over-the-counter antacid with an acid neutralizing capacity of 38.8 mEq/10 mL. Single doses up to 30 mL are often administered for acute symptomatic relief. Because of the acute nature of its mechanism of action, Maalox Max® was administered, immediately prior to saxagliptin administration.

Famotidine is an over-the-counter antacid that inhibits gastric acid secretion via competition for H₂-receptor binding with histamine. Famotidine is typically administered 20 to 40 mg once or twice daily with a maximal pharmacodynamic effect occurring 1-3 hours after dosing. To account for the delay in onset of action, famotidine (40 mg tablet) was administered 3 hours prior to saxagliptin dosing.

Omeprazole is an over-the-counter Proton Pump Inhibitor that inhibits gastric acid secretion by irreversibly binding to and disturbing the function of the proton pump (H⁺/K⁺- ATPase). The dose of 40 mg of omeprazole administered every 24 hours was selected because it is the highest recommended starting dose and it is highly effective, producing a 90% decrease in both basal and peak acid output. Omeprazole was administered for 4 days prior to saxagliptin administration.

The primary objective was to determine the effect of Maalox Max®, famotidine, and omeprazole on the single dose PK of 10 mg of saxagliptin. This was an open-label, randomized, five-treatment, five-period, unbalanced, three-way crossover study in healthy subjects. The treatments administered were:

- Treatment A: Single dose of 10 mg of saxagliptin on Day 1
- Treatment B: Co-administration of a single dose of 10 mg of saxagliptin + 30 ml Maalox Max® on Day 1 (Maalox Max® was administered immediately prior to saxagliptin)
- Treatment C: Single dose of 10 mg of saxagliptin 3 hours after administration of 40 mg famotidine on Day 1
- Treatment D: Single dose of 40 mg of omeprazole for 4 days (Days 1-4)
- Treatment E: Co-administration of a single dose of 10 mg of saxagliptin + a single dose of 40 mg of omeprazole on Day 1.

Compared to when saxagliptin was administered alone, the C_{max} for saxagliptin was 25.9% lower when saxagliptin was co-administered with Maalox Max® with the 90% confidence interval for the ratio of the geometric means (0.651, 0.845) falling outside the 80% to 125% limit. However; for AUC (0-T) and AUC(INF) of saxagliptin, the 90% CI for the ratio of geometric means were contained within the pre-specified 80% to 125% no-effect limit thus meeting the criteria for concluding absence of effect.

Compared to when saxagliptin was administered alone, the AUC (0-T) and AUC(INF) of saxagliptin administered 3h after famotidine satisfied the criterion for concluding absence of effect. The geometric mean C_{max} was 13.7% higher when saxagliptin was administered 3h after famotidine, and the 90% CI for the ratio of geometric means extended slightly above the pre-specified no-effect limit of 80% to 125%.

Compared to when saxagliptin was administered alone neither C_{max}, nor AUC(0-T) or AUC(INF) were different when saxagliptin was co-administered with omeprazole.

Table: Summary statistics for saxagliptin PK parameters

Pharmacokinetic Parameter	Treatment			
	A (n=15)	B (n=15)	C (n=15)	E (n=15)
Cmax (ng/mL)				
Geometric Mean (CV %)	45.02 (28)	33.53 (34)	51.13 (33)	44.01 (33)
Tmax (h)				
Median (min, max)	0.50 (0.50, 1.00)	1.00 (0.25, 2.50)	0.50 (0.50, 1.00)	1.00 (0.50, 2.50)
AUC(0-T) (ng·h/mL)				
Geometric Mean (CV %)	144.65 (19)	137.77 (18)	148.60 (19)	162.38 (16)
AUC(INF) (ng·h/mL)				
Geometric Mean (CV %)	150.43 (19)	145.09 (17)	154.16 (17)	169.13 (16)
T-HALF (h)				
Mean (SD)	2.35 (0.29)	3.26 (0.97)	2.42 (0.26)	2.47 (0.41)

Results of statistical analyses for effect of Maalox Max, famotidine and omeprazole on saxagliptin PK parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adjusted Geometric Mean (B/A) Point Estimate (90% CI)
	Treatment A (n = 15)	Treatment B (n = 15)	
C _{max} (ng/mL)	45.02	33.38	0.741 (0.651, 0.845)
AUC(0-T) (ng·h/mL)	144.66	137.77	0.952 (0.914, 0.993)
AUC(INF) (ng·h/mL)	150.43	145.09	0.965 (0.926, 1.005)
Pharmacokinetic Parameter	Treatment A (n = 15)	Treatment C (n = 15)	Ratios of Adjusted Geometric Mean (C/A) Point Estimate (90% CI)
	C _{max} (ng/mL)	51.18	1.137 (0.998, 1.295)
AUC(0-T) (ng·h/mL)	144.66	148.60	1.027 (0.985, 1.071)
AUC(INF) (ng·h/mL)	150.43	154.17	1.025 (0.984, 1.067)
Pharmacokinetic Parameter	Treatment A (n = 15)	Treatment E (n = 15)	Ratios of Adjusted Geometric Mean (E/A) Point Estimate (90% CI)
	C _{max} (ng/mL)	44.01	0.977 (0.858, 1.114)
AUC(0-T) (ng·h/mL)	144.66	162.88	1.125 (1.080, 1.174)
AUC(INF) (ng·h/mL)	150.43	169.18	1.125 (1.080, 1.171)

The sponsor did not conduct any statistical analysis for the PK parameters of BMS-510849. The changes in plasma exposures of BMS-510849 in general were similar to that of saxagliptin when co-administered with these agents as compared to saxagliptin given alone.

Comments:

- The solubility of saxagliptin decreases approximately 7-fold between pH 6 and 8. *In vitro* testing with saxagliptin indicates that solubility increases from 130 mg/mL at pH 2 to a maximum concentration of 150 mg/mL at pH 6, and decreases to a low of 20 mg/mL at pH 8. This study evaluated the three classes of compounds that are known to interact with drugs that are sensitive to change in gastric pH.
- Famotidine is a potent inhibitor of human organic cation transporter protein-3 (hOCT-3) and a moderate inhibitor of hOCT-1 and hOCT-2. On the basis of a lack of a substantial PK interaction between saxagliptin and famotidine it appears unlikely that the PK of saxagliptin is affected by inhibition of hOCT-1, hOCT-2 or hOCT-3.
- Omeprazole has been shown to be a modest substrate for Pgp and an inducer for multi drug resistance protein-3 (MRP-3). Since no substantial difference in the PK of saxagliptin or BMS-510849 was observed when saxagliptin was co-administered with omeprazole neither compound is likely to be an *in vivo* substrate for either Pgp or MRP-3.

Clinical study CV181017: Drug interaction study of saxagliptin and metformin in healthy subjects (Aug-Sept 2004)

The primary objectives of this study were to determine the effect of metformin on the pharmacokinetics of saxagliptin when co-administered in healthy subjects and vice-versa. This was an open-label, randomized, three-period, three-treatment, crossover study balanced for residual effects. 18 Subjects (2 discontinued) were randomized to receive the following three treatments in one of six treatment sequences:

- Treatment A = Single oral dose of 100 mg saxagliptin
- Treatment B = Single oral dose of 1000 mg metformin
- Treatment C = Co-administration of single oral doses of 100 mg saxagliptin and 1000 mg metformin.

When 100 mg saxagliptin was co-administered with 1000 mg metformin, the geometric means for C_{max} was decreased by 21% and the 90%CI fell outside of the 80-125% interval. There was no change in the AUC_{inf} or AUC_{0-t} with or without metformin. In case of BMS-510849, although there was a 12% decrease in its C_{max} when co-administered with metformin, the 90% CI was within the pre-specified limits for AUC and C_{max}.

Table: Summary statistics for saxagliptin PK parameters

Pharmacokinetic Parameter	Treatment	
	A (n=16)	C (n=16)
C _{max} (ng/mL) Geometric Mean (C.V. %)	640 (21)	493 (27)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	2048 (23)	1989 (21)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	2007 (24)	1947 (21)
T _{max} (h) Median (Min, Max)	0.75 (0.50, 1.50)	0.75 (0.50, 3.00)
T-HALF (h) Mean (S.D.)	2.65 (0.52)	2.88 (0.50)

Treatments: A = 100 mg saxagliptin

C = 100 mg saxagliptin + 1000 mg metformin

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means (C/A)	
	A	C	Point Estimate	90% C.I
C _{max} (ng/mL)	635	499	0.79	(0.71, 0.87)
AUC(INF) (ng·h/mL)	2028	1986	0.98	(0.93, 1.04)
AUC(0-T) (ng·h/mL)	1987	1945	0.98	(0.92, 1.04)

Table: Summary statistics for BMS-510849 PK parameters

Pharmacokinetic Parameter	Treatment	
	A (n=16)	C (n=16)
C _{max} (ng/mL) Geometric Mean (C.V. %)	866 (40)	767 (39)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	5128 (31)	5066 (33)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	5022 (32)	4952 (33)
T _{max} (h) Median (Min, Max)	1.50 (1.00, 4.00)	2.00 (1.00, 4.00)
T-HALF (h) Mean (S.D.)	3.76 (0.60)	4.28 (0.38)

Treatments: A = 100 mg saxagliptin

C = 100 mg saxagliptin + 1000 mg metformin

When 100 mg saxagliptin was co-administered with 1000 mg metformin, the geometric means for C_{max}, AUC(INF) and AUC(0-T) of metformin increased by 9%, 20%, and 20%, respectively, relative to those observed following administration of 1000 mg metformin alone. However, the 90% CI for the ratios of geometric means with and without saxagliptin were within the 80-125% interval.

Table: Summary statistics for metformin PK parameters

Pharmacokinetic Parameter	Treatment	
	B (n=16)	C (n=16)
C _{max} (ng/mL) Geometric Mean (C.V. %)	1615 (17)	1768 (24)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	10022 (13)	12014 (16)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	9862 (13)	11868 (16)
T _{max} (h) Median (Min, Max)	2.00 (1.00, 4.00)	3.00 (0.75, 4.00)
T-HALF (h) Mean (S.D.)	7.00 (3.34)	6.24 (3.44)

Comments:

- 100 mg saxagliptin was used in this study.
- Data from *in vitro* studies that metformin is a substrate for organic cation transport protein-1 (OCT-1) and -2 (OCT-2) in liver and kidneys, respectively, Saxagliptin and BMS-510849 did not appear to inhibit OCT-1 and 2 in this study. Also, *in vitro*, neither saxagliptin nor BMS-510849 is a substrate for OCT1 and OCT2.

Clinical Study CV181005 STUDY: Effect of ketoconazole on the pharmacokinetics of BMS-477118 in healthy subjects (Jul-Aug 2004)

The primary objective of this study was: To assess the effects of ketoconazole on the pharmacokinetics of a single oral dose of saxagliptin, in healthy subjects. This was an open-label, non-randomized, single-sequence study in 16 healthy subjects. The treatments were administered as follows:

Study Day	Treatment	Total Daily Oral Dose	Number/Strength of Tablets
1	A	100 mg saxagliptin	2 x 40 mg and 4 x 5 mg saxagliptin
3-8	B	400 mg ketoconazole	1 x 200 mg ketoconazole q12h
9	C	100 mg saxagliptin 400 mg ketoconazole	2 x 40 mg and 4 x 5 mg saxagliptin and 1 x 200 mg ketoconazole q12h
10-11	D	400 mg ketoconazole	1 x 200 mg ketoconazole q12h

When a single dose of 100 mg saxagliptin was co-administered with 200 mg ketoconazole q12h, the geometric means for C_{max}, AUC(INF) and AUC(0-T) of saxagliptin increased by 62%, 145%, and 148%, respectively, relative to those observed following administration of 100 mg saxagliptin single dose alone. The 90% CI for the ratios were beyond the 80-125% limit.

Table: Summary statistics for saxagliptin PK

Saxagliptin Pharmacokinetic Parameter	Treatment	
	A (n=15)	C (n=15)
C _{max} (ng/mL) Geometric Mean (C.V. %)	546 (26)	837 (25)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	1972 (24)	4823 (17)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	1924 (25)	4780 (17)
T _{max} (h) Median (Min, Max)	1.00 (0.50, 1.00)	1.00 (0.50, 2.50)
T _{1/2} (h) Mean (S.D.)	2.37 (0.42)	3.46 (0.38)

Saxagliptin Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (Day 9/ Day 1)	
	Day 1	Day 9	Point Estimate	90% C.I
C _{max} (ng/mL)	546	837	1.62	(1.47, 1.80)
AUC(INF) (ng·h/mL)	1972	4823	2.45	(2.30, 2.60)
AUC(0-T) (ng·h/mL)	1924	4780	2.48	(2.33, 2.65)

Treatment: A = 100 mg saxagliptin single dose

Treatment: C = 100 mg saxagliptin single dose + 200 mg ketoconazole q12h

On the other hand, when a single dose of 100 mg saxagliptin was co-administered with 200 mg ketoconazole q12h, the geometric means for C_{max}, AUC(INF) and AUC(0-T) of BMS-510849 decreased by 95%, 88%, and 91%, respectively, relative to those observed following administration of 100 mg saxagliptin single dose alone.

Table: Summary statistics for BMS-510849 PK

BMS-510849 Pharmacokinetic Parameter	Treatment	
	A (n=15)	C (n=15)
C _{max} (ng/mL) Geometric Mean (C.V. %)	999 (24)	53 (49)
AUC(INF) (ng·h/mL) Geometric Mean (C.V. %)	5381 (19)	627 (43)
AUC(0-T) (ng·h/mL) Geometric Mean (C.V. %)	5294 (19)	473 (50)
T _{max} (h) Median (Min, Max)	1.50 (1.00, 2.00)	2.00 (0.75, 4.00)
T _{1/2} (h) Mean (S.D.)	3.68 (0.53)	6.33 (2.49)

BMS-510849 Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (Day 9/Day 1)	
	Day 1	Day 9	Point Estimate	90% C.I
C _{max} (ng/mL)	999	53	0.05	(0.05, 0.05)
AUC(INF) (ng·h/mL)	5381	627	0.12	(0.10, 0.13)
AUC(0-T) (ng·h/mL)	5294	473	0.09	(0.07, 0.11)

Treatment: A = 100 mg saxagliptin single dose

Treatment: C = 100 mg saxagliptin single dose + 200 mg ketoconazole q12h

Adverse events: 14 of 15 subjects experienced a decline in lymphocyte count on Day 10 following administration of a single dose of 100 mg saxagliptin + 200 mg ketoconazole q12h (Treatment C). Pyrexia, chills, and decreased lymphocytes appeared after the second dose of 100 mg saxagliptin, which was administered 8 days after the first 100 mg dose of saxagliptin in this study. The second 100 mg dose was co-administered with ketoconazole doses to steady-state which suggests the combination of saxagliptin and ketoconazole may be implicated in the appearance of pyrexia, chills and lymphocyte findings.

Comments:

- 100 mg dose of saxagliptin was used as substrate in this study. A increase in exposure of saxagliptin was seen (~ 2.5 fold) in presence of ketoconazole.

- Highest total daily dose of 400 mg ketoconazole was selected to provide maximum amount of CYP3A inhibition. Twice daily dosing regimen was used (200 mg q12h).
- Ketoconazole was in steady-state prior to assessing interaction. Trough plasma sampling confirmed this. When a single dose of 100 mg saxagliptin was co-administered with 200 mg ketoconazole q12h, the geometric means for C_{max}, AUC(INF) and AUC(0-T) of ketoconazole decreased by 16% and 13%, respectively, relative to those observed following administration of 200 mg ketoconazole q12h alone.
- The sponsor used a very high dose of the substrate (saxagliptin) in this DDI study. There was about 2.5 fold increase in AUC when 100 mg saxagliptin was used along with ketoconazole. In other study, the sponsor used 20 mg saxagliptin with ketoconazole and there was a 3.8 fold increase in AUC. When diltiazem was used in a DDI study with 10 mg saxagliptin there was a 2.1 fold increase in AUC. The proposed clinical dose for saxagliptin is 5 mg.

Study #	Year	Saxagliptin Dose	CYP3A Inhibitor	AUC-fold change	C _{max} -fold change
CV181005	2004	100 mg	Ketoconazole (200 mg q 12h)	2.5	63% ↑
CV181022	2004	20 mg	Ketoconazole (200 mg q 12h)	3.8	2.44
CV181053	2007	10 mg	Diltiazem (360 mg QD)	2.1	63% ↑

Clinical Study CV181028: Pharmacokinetic drug interaction study with saxagliptin and pioglitazone in healthy subjects (Oct 2005)

The primary objectives were to determine the effect of saxagliptin on the PK of pioglitazone, when co-administered in healthy subjects and to determine the effect of pioglitazone on the PK of saxagliptin, when co-administered in healthy subjects.

This was an open-label, non-randomized, sequential study in healthy subjects. All study treatments were administered following a fast of at least 10 hours. All subjects received the following three treatments:

Treatment A: 10 mg saxagliptin (Days 1 to 3)

Treatment B: 45 mg pioglitazone (Days 4 to 8)

Treatment C: 10 mg saxagliptin + 45 mg pioglitazone (Days 9 to 13)

Although the geometric mean for both C_{max} and AUC(TAU) of saxagliptin increased by 11%, when saxagliptin was co-administered with pioglitazone, the 90% confidence intervals for the ratios of population geometric means, with and without pioglitazone, were within the 80% to 125% no-effect interval for both AUC and C_{max}.

Summary Statistics for Saxagliptin Pharmacokinetic Parameters Excluding Subject CV181028-1-24

Pharmacokinetic Parameter	Treatment	
	A (n=27)	C (n=27)
C _{max} (ng/mL)		
Geometric Mean (CV %)	46 (24)	51 (29)
AUC(TAU) (ng·h/mL)		
Geometric Mean (CV %)	176 (19)	196 (21)
T _{max} (h)		
Median (Min, Max)	0.50 (0.50, 1.00)	1.00 (0.50, 2.50)

Treatments: A = 10 mg saxagliptin

C = 10 mg saxagliptin + 45 mg pioglitazone

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (Trt C / Trt A)	
	Trt A	Trt C	Point Estimate	90% CI
C _{max} (ng/mL)	46	51	1.11	(1.03, 1.20)
AUC(TAU) (ng·h/mL)	176	196	1.11	(1.06, 1.16)

Summary Statistics for BMS-510849 Pharmacokinetic Parameters Excluding Subject CV181028-1-24

Pharmacokinetic Parameter	Treatment	
	A (n=27)	C (n=27)
C _{max} (ng/mL)		
Geometric Mean (CV %)	119 (25)	120 (25)
AUC(TAU) (ng·h/mL)		
Geometric Mean (CV %)	588 (23)	628 (25)
T _{max} (h)		
Median (Min, Max)	1.50 (1.00, 3.00)	1.50 (1.00, 3.00)

When 10 mg saxagliptin was co-administered with 45 mg pioglitazone, the geometric means for C_{max} and AUC(TAU) of pioglitazone increased by 14% and 8%, respectively, relative to those observed following administration of 45 mg pioglitazone alone. The 90% confidence interval for the ratios of population geometric means, with and without saxagliptin, were within the 80% to 125% no-effect interval for AUC(TAU) of pioglitazone. However, the 90% confidence interval for the ratios of population geometric means, with and without saxagliptin, extended slightly above the 80% to 125% no-effect interval for C_{max} of pioglitazone. The pharmacokinetic parameters for hydroxy-pioglitazone were similar following the administration of 45 mg pioglitazone alone and following the co-administration of 10 mg saxagliptin and 45 mg pioglitazone.

Comments:

- A 10 mg dose of saxagliptin is the highest dose that was studied in the clinical development program and 45 mg of pioglitazone is the highest recommended dose.

- To account for a possible interaction upon co-administration with saxagliptin, 45 mg of pioglitazone was administered for another 5 days, allowing for the re-establishment of steady-state concentrations of both pioglitazone and the M-IV metabolite.
- The sponsor used summary statistics and statistical analyses for saxagliptin and BMS-510849 that excluded the data from Subject CV181028-1-24 (had very low saxagliptin and BMS-510849 exposures) and these were considered to be the most accurate representation of the pharmacokinetic results.
- The median and range for the T_{max} of saxagliptin and BMS-510849 appeared to be unaffected by co-administration of pioglitazone. All PK parameters for BMS-510849 appeared to be unaffected by the co-administration of pioglitazone.
- Co-administration of saxagliptin to steady-state increased the C_{max} of pioglitazone at steady-state by 14% (90% CI for ratios of population geometric means with and without saxagliptin: 1.03 to 1.28).

Clinical Study CV181033: Pharmacokinetic drug interaction study with saxagliptin and simvastatin in healthy subjects (Dec 2005 – Jan 2006)

The main objective was to determine the effect of saxagliptin on the pharmacokinetics of simvastatin and vice-versa when co-administered in healthy subjects. The effect on the PK of metabolites BMS-510849 and simvastatin acid was also determined. This was an open-label, non-randomized, sequential study in healthy subjects. Subjects were administered four daily doses of 10 mg saxagliptin. PK sampling was done at trough concentrations on Days 2-4 and serial sampling on Day 4. On day 5, subjects began receiving 40 mg QD simvastatin for 4 days and blood sampling was done on Days 7-9 for trough and serial sampling on Day 8. On Days 9-12 subjects received both simvastatin and saxagliptin and plasma sampling was done at trough (Days 10-12) and on Day 12 at various time-points. On Days 4, 8, and 12, subjects were maintained in a fasted state for 4 hours post-dose. (24 enrolled; 23 completed).

When co-administered with simvastatin, the geometric means for C_{max} and AUC(τ) of saxagliptin increased by 21% and 12%, respectively, relative to those observed following administration of 10 mg saxagliptin alone. The 90% confidence intervals for the ratio of population geometric means, with and without simvastatin, were within the prespecified confidence interval (80% to 125%) for AUC(τ) of saxagliptin but not for its C_{max}.

Table: Summary statistics for saxagliptin PK parameters

Parameters		Treatment	
PK Parameter		A (n=23)	C (n=23)
C _{max} (ng/mL)	Geometric Mean (CV %)	44 (32)	54 (39)
AUC(TAU) (ng·h/mL)	Geometric Mean (CV %)	153 (19)	172 (17)
T _{max} (h)	Median (Min, Max)	1.00 (0.50, 2.00)	0.50 (0.25, 2.00)

PK Parameter	Geometric Means		Ratio of Geometric Means (Trt C / Trt A)	
	Trt A	Trt C	Point Estimate	90% CI
C _{max} (ng/mL)	44	54	1.21	(1.11, 1.31)
AUC(TAU) (ng·h/mL)	153	172	1.12	(1.09, 1.15)

Treatments: A = 10 mg saxagliptin (Day 4)

C = 10 mg saxagliptin + 40 mg simvastatin (Day 12)

There was no effect of simvastatin on the PK of BMS-510849. The 90% CI for the ratio of population geometric means for both C_{max} and AUC(TAU), with and without simvastatin, were within the prespecified confidence interval (80% to 125%).

Table: Summary statistics for BMS-510849 PK parameters

PK Parameter	Treatment	
	A (n=23)	C (n=23)
C _{max} (ng/mL)		
	Geometric Mean (CV %)	96 (33) / 103 (29)
AUC(TAU) (ng·h/mL)		
	Geometric Mean (CV %)	529 (26) / 538 (24)
T _{max} (h)		
	Median (Min, Max)	1.50 (1.00, 2.00) / 1.50 (1.00, 2.00)

When 10 mg saxagliptin was co-administered with 40 mg simvastatin, the geometric mean C_{max} of simvastatin decreased by 12% and the geometric mean AUC(TAU) of simvastatin acid increased by 16%, relative to those observed following administration of 40 mg simvastatin alone. There was no change in the AUC_{tau} of simvastatin or C_{max} for simvastatin acid when co-administered with saxagliptin.

Comments:

- Both agents share a common metabolic pathway (CYP3A4) and DDI was assessed at steady-state for both agents. There was an effect on the C_{max} of saxagliptin (21% increase) with no change in its AUC or on BMS-510849 PK parameters.
- The sponsor used a wider 90% CI for simvastatin and simvastatin acid (70-143%). Based on the 80-125%, the C_{max} of simvastatin was about 12% lower and the AUC_{tau} of simvastatin acid was 16% higher in presence of saxagliptin.
- No dosage adjustments are recommended in this case.

Clinical Study CV181052: Pharmacokinetic drug interaction study with saxagliptin and digoxin in healthy subjects (May-Jun 2006)

The main objective was to determine the effect of digoxin on the pharmacokinetics of saxagliptin in healthy subjects (20 enrolled; 14 randomized and completed) and to determine the effect of saxagliptin on the PK of digoxin in healthy subjects. This was an open-label, randomized, three-period, three-treatment, crossover study in healthy subjects. Each subject received the following three treatments during the course of the study according to the randomization schedule:

- Single oral dose of saxagliptin 2 x 5 mg tablets (Treatment A)
- 0.25 mg digoxin tablet q6h on Day 1 followed by 0.25 mg digoxin tablet q12h on Day 2 followed by 0.25 mg digoxin tablet QD on Days 3-7 (Treatment B)
- Single oral dose of 2 x 5 mg saxagliptin tablets and 0.25 mg digoxin tablet q6h on Day 1 followed by a single oral dose of 2 x 5 mg saxagliptin tablets and 0.25 mg digoxin tablet q12h on Day 2 followed by 2 x 5 mg saxagliptin tablets and 0.25 mg digoxin tablet QD on Days 3-7 (Treatment C)

On Day 1 of Period 1, subjects were randomized to one of the two possible treatment sequences (ABC or ACB). The washout between Periods 1 and 2 was at least 1 day. The washout between Periods 2 and 3 was at least 2 weeks. Subjects were required to fast for 8 hours prior to dosing.

There was no effect of digoxin on saxagliptin AUC and Cmax when co-administered. Similarly, there was no effect on the PK parameters of BMS-510849.

Table: Summary statistics for saxagliptin PK parameters

Pharmacokinetic Parameter	Treatment A (n = 14)	Treatment C (n = 14)
C _{max} (ng/mL) Geometric Mean (CV%)	52 (24)	51 (25)
AUC(TAU) (ng·h/mL) Geometric Mean (CV%)	N/A	185 (23)
AUC(INF) (ng·h/mL) Geometric Mean (CV%)	177 (26)	N/A
T _{max} (h) Median (min, max)	0.50 (0.50, 1.50)	0.50 (0.50, 2.00)
T _{1/2} (h) Mean (SD)	2.55 (0.44)	2.80 (0.87)

When digoxin was co-administered with saxagliptin (Treatment C) compared to digoxin administered alone (Treatment B), the geometric means of C_{max} and AUC(TAU) for

digoxin were 9% and 6% higher respectively. The results for both Cmax and AUC(TAU) satisfied the pre-specified criterion.

Table: Summary statistics for digoxin PK parameters

Pharmacokinetic Parameter	Treatment B (n = 14)	Treatment C (n = 14)
Cmax (ng/mL) Geometric Mean (CV%)	1.49 (20)	1.62 (20)
AUC(TAU) (ng•h/mL) Geometric Mean (CV%)	15 (28)	16 (24)
Tmax (h) Median (min, max)	1.50 (0.50, 3.00)	1.50 (0.50, 4.00)
T-Half (h) Mean (SD)	17.49 (7.41)	22.64 (14.93)

Comments:

- Steady-state assessment was done for both agents. The 0.25 mg q6h and 0.25 mg q12h loading doses and 0.25 mg QD maintenance dose of digoxin were selected for this study to achieve adequate digitalization and to achieve clinically-relevant digoxin concentrations and which will not be toxic to healthy subjects.
- No significant interaction was demonstrated in this study indicating that any interaction mediated through P-glycoprotein is unlikely.
- No dosage adjustment of either saxagliptin or digoxin is necessary when these two drugs are co-administered.

Clinical Study Report for Study CV181027

ABBREVIATED REPORT

TITLE OF STUDY: Pharmacokinetic drug interaction study with saxagliptin and digoxin in healthy subjects (Feb-Mar 2006)

This study was intended to evaluate the effect of saxagliptin on the pharmacokinetics of digoxin and the effect of digoxin on the PK of saxagliptin and its pharmacologically active metabolite, BMS-510849. Additionally, the safety of the saxagliptin alone or in combination with digoxin was assessed. All 7 subjects randomized to Treatment C (digoxin + saxagliptin) in Period 2 did not receive their saxagliptin dose on Day 4. The

Sponsor made the decision to stop the study prematurely because of this significant protocol deviation. The PK results were not analyzed due to the omission of the saxagliptin dose on Day 4. Full safety data was included in this report. Sponsor has stated that the concomitant administration was well tolerated and safe. The study was repeated (CV181052).

Perturber	Substrate	GMR (90% CI)	
		AUC	Cmax
Saxagliptin 10 mg	Glyburide 5mg (2C9)	1.06 (1.00 – 1.13)	1.16 (1.06 – 1.28)
	Saxagliptin	0.98 (0.95 - 1.01)	1.08 (1.02 – 1.14)
Maalox max 30 mL administered immediately prior to saxagliptin	Saxagliptin 10 mg	0.95 (0.91 – 0.99)	0.74 (0.65 – 0.84)
Famotidine 40 mg given 3 h prior to saxagliptin	Saxagliptin 10 mg	1.02 (0.98 – 1.07)	1.13 (0.99 – 1.29)
Omeprazole 40 mg QD (Days 1-4) prior to saxagliptin	Saxagliptin 10 mg	1.12 (1.08 – 1.17)	0.97 (0.85 – 1.11)
Saxagliptin 100 mg	Metformin 1000 mg	1.20 (1.17 – 1.24)	1.09 (1.01 – 1.19)
	Saxagliptin	0.98 (0.92 – 1.04)	0.79 (0.71 – 0.87)
	BMS-510849	0.99 (0.95 – 1.02)	0.88 (0.82 – 0.94)
Saxagliptin 10 mg QD (Days 1-3) and then (Days 9-13)	Pioglitazone 45 mg (Days 4-13)	1.08 (0.99 – 1.17)	1.14 (1.03 – 1.27)
	Saxagliptin	1.11 (1.06 – 1.16)	1.11 (1.03 – 1.20)
Saxagliptin 10 mg QD (Days 1-4) and (Days 9-12)	Simvastatin mg (3A4) (Days 5-12)	1.04 (0.94 – 1.15)	0.88 (0.74 – 1.06)
	Simvastatin acid	1.16 (1.04 – 1.29)	1.00 (0.89 – 1.13)
	Saxagliptin	1.12 (1.09 – 1.15)	1.21 (1.11 – 1.31)
	BMS-510849	1.02 (0.99 – 1.05)	1.08 (1.02 – 1.14)
Saxagliptin 10 mg (Day 1-7)	Digoxin (Day 1, 0.25 mg q6h; Day 2, 0.25 mg q 12h; Days 3-7 0.25 mg QD)	1.06 (1.02 – 1.11)	1.09 (1.00 – 1.19)
	Saxagliptin	1.05 (0.99 – 1.11)	0.99 (0.87 – 1.12)
	BMS-510849	1.06 (1.01 – 1.12)	1.02 (0.91 – 1.14)
Ketoconazole 200 mg q12 h for 6 days (3A4)	Saxagliptin 100 mg	2.48 (2.33 – 2.65)	1.62 (1.47 – 1.80)
	BMS-510849	0.09 (0.07 – 0.11)	0.05 (0.05 – 0.06)
	Ketoconazole	0.87 (0.79 – 0.95)	0.84 (0.77 – 0.92)
Ketoconazole 200 mg q12 h for 6 days (3A4)	Saxagliptin 20 mg	3.79 (3.39 – 4.24)	2.44 (2.03 – 2.93)

Rifampicin	Saxagliptin BMS-510849		
Diltiazem (3A4) 360 mg (Days 2-9)	Saxagliptin 10 mg (Day 1 and Day 9)	2.13 (1.99 – 2.28)	1.63 (1.40 – 1.89)
	BMS-510849	0.64 (0.59 – 0.69)	0.56 (0.49 – 0.64)
	Diltiazem	1.10 (0.97 – 1.25)	1.16 (0.98 – 1.36)

Bolded values indicate out of BE criteria.

CV181059 STUDY: Effects of Rifampin on the Single-dose Pharmacokinetics of Saxagliptin in Healthy

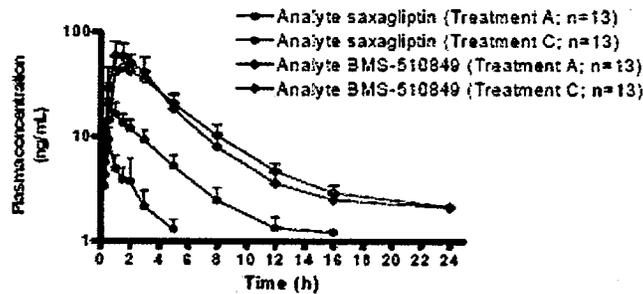
STUDY PERIOD: Study Date: 14-Mar-2008 - 11-Apr-2008

The main objective was to assess the effect of rifampin on the single dose pharmacokinetics of saxagliptin, when rifampin and saxagliptin are co-administered to healthy subjects. Secondary objectives include the effect of rifampin on BMS-510849 as well as on PD (DPP-4 inhibition).

This was a non-randomized, open-label, single sequence study in healthy subjects. Fourteen subjects received a single oral dose of 5 mg saxagliptin on Day 1, 600 mg once-daily oral doses of rifampin on Days 2 to 6, and a single oral dose of 5 mg saxagliptin concomitantly with a single oral dose of 600 mg rifampin on Day 7. Subjects were confined to the clinical facility for the duration of the study. Subjects were discharged from the clinical facility after the PK collection and all safety assessments were completed on Day 8. Blood and urine samples were collected for PK and PD analysis for up to 24 hours post-dose on Day 1 and up to 24 hours post-dose on Day 7.

The results suggest that co-administration of rifampin substantially reduces saxagliptin exposures. When 5 mg saxagliptin was co-administered with 600 mg rifampin, the geometric means for C_{max}, AUC_{inf} and AUC_{0-t} of saxagliptin decreased by 53%, 76% and 80%, respectively, relative to those observed following administration of 5 mg saxagliptin alone.

Figure: Mean (+SD) plasma concentration-time profiles of following a single dose of 5 mg saxagliptin and BMS-510849 administered with and without 600 mg rifampin once daily



The 90% confidence intervals for the ratios of population geometric means, with and without rifampin, were entirely below the (80%, 125%) no-effect interval for C_{max}, AUC_{inf} and AUC_{0-t} of saxagliptin. No changes in the renal clearance values of saxagliptin were observed when saxagliptin was administered with and without rifampin treatment.

Table: Summary statistics for saxagliptin pharmacokinetic parameters and statistical analyses

Pharmacokinetic Parameter	Treatment	
	5 mg Saxagliptin (n=13)	5 mg Saxagliptin with 600 mg Rifampin (n=13)
C _{max} (ng/mL)	20 (47)	9 (25)
Geometric Mean (CV%)		
AUC (INF) (ng·h/mL)	73 (26)	17 (24)
Geometric Mean (CV%)		
AUC(0-t) (ng·h/mL)	66 (28)	13 (33)
Geometric Mean (CV%)		
T _{max} (h)	0.48 (0.46, 2.02)	0.48 (0.46, 1.98)
Median (Min, Max)		
T-1/2 (h)	3.02 (0.64)	1.70 (0.57)
Mean (SD)		
UR (%)	17 (4)	4 (1)
Mean (SD)		
CLR (mL/min)	180 (29)	197 (15)
Geometric Mean (CV%)		

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (5 mg Saxagliptin with 600 mg Rifampin/5 mg Saxagliptin)	
	Saxagliptin 5 mg	Saxagliptin 5 mg + Rifampin 600 mg	Point Estimate	90% CI
C _{max} (ng/mL)	20	9	0.47	(0.38, 0.57)
AUC (INF) (ng·h/mL)	73	17	0.24	(0.21, 0.27)
AUC(0-t) (ng·h/mL)	66	13	0.20	(0.17, 0.25)

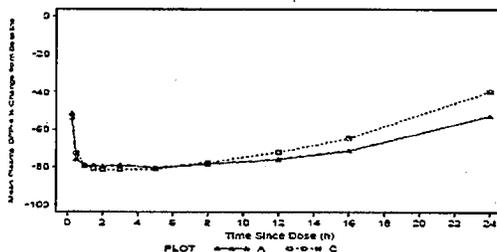
When 5 mg saxagliptin was co-administered with 600 mg rifampin, the geometric means for C_{max}, AUC_{inf} and AUC_{0-t} of BMS-510849 increased by 39%, 3% and 4%, respectively, relative to those observed following administration of 5 mg saxagliptin alone. The 90% confidence interval for the ratio of population geometric means, with and without rifampin, extends above the (80%, 125%) interval for C_{max} of BMS-510849 while there was no effect on AUC. No changes in the renal clearance values of BMS-510849 were observed when saxagliptin was administered with and without rifampin treatment.

Table: Results of Statistical Analyses on BMS-510849 C_{max}, AUC_{inf} and AUC(0-t)

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (5 mg Saxagliptin with 600 mg Rifampin/5 mg Saxagliptin)	
	Saxagliptin 5 mg	Saxagliptin 5 mg + Rifampin 600 mg	Point Estimate	90% CI
C _{max} (ng/mL)	49	88	1.39	(1.23, 1.56)
AUC _(INF) (ng·h/mL)	258	266	1.03	(0.97, 1.09)
AUC _(0-T) (ng·h/mL)	241	251	1.04	(0.98, 1.11)

The maximum inhibition of DPP4 activity (%I_{max}) remained unchanged when saxagliptin was administered with (I_{max} = 83.2%) or without (I_{max} = 83.1%) rifampin. The overall inhibition of DPP4 activity over the dosing interval AUEC(0-24h) was 6% lower when saxagliptin was administered with rifampin compared to when saxagliptin was administered alone. The mean DPP4 inhibition for the trough sample (24 h post dose with saxagliptin) was around 13% lower when saxagliptin was co-administered with rifampin relative to saxagliptin alone.

Mean Plasma DPP4 % Change from Baseline versus Time Profiles in the Absence and Presence of Rifampin Induction



Comments:

- Both the inducer and substrate were dosed at the exposures that are relevant to the clinical use; highest dose of substrate was used (5 mg).
- Rifampin was dosed for 5 days prior to co-administration with saxagliptin, which is sufficient for full induction potential of rifampin.
- Total active moiety exposure was calculated by adding the molar AUC_{inf} of saxagliptin and one half of the molar AUC_{inf} of BMS-510849 (one half of BMS-510849 was used since it has 2-fold lower K_i for DPP-4 inhibition as compared to parent).
- Decrease in saxagliptin exposure can be mainly attributed to induction of CYP3A4/3A5 mediated metabolism of saxagliptin. Induction also resulted in a decrease in half life from 3.02 to 1.7 h. This metabolic induction is also evident in a 5-fold increase in the metabolite-to-parent AUC_{inf} ratio.
- Rifampin also inhibits certain uptake transporters (OATP1, MRP2). The decrease in exposure of saxagliptin could also be due to inhibition of an uptake transporter(s) that may facilitate absorption of saxagliptin.

- The mean DPP4 inhibition for the trough sample (24 h post dose with saxagliptin) was around 13% lower when saxagliptin was co-administered with rifampin relative to saxagliptin alone. The clinical significance of these changes is unknown.

TITLE OF STUDY: *The Safety and Pharmacokinetics of Saxagliptin (BMS-477118) in Subjects with Normal Renal Function, Mild, Moderate, and Severe Renal Impairment, and in Hemodialysis Subjects.*

Duration: 3/24/06 – 1/29/08

Primary Objective: To determine the effects of various degrees of renal function impairment and hemodialysis on the single oral dose pharmacokinetics of saxagliptin (BMS-477118) and its pharmacologically active metabolite, BMS-510849.

Method: This was an open-label, parallel group, single-dose study in male and female subjects (ages 24-79 years; BMI 20-2 – 39.8 Kg/m²). Subjects were classified into one of the following five groups (8 subjects/group) according to their degree of renal function.

- A: Normal renal function (creatinine clearance (CLcr) > 80 mL/min)
- B: Mild renal impairment (50 < CLcr ≤ 80 mL/min)
- C: Moderate renal impairment (30 ≤ CLcr ≤ 50 mL/min)
- D: Severe renal impairment (CLcr < 30 mL/min and not on dialysis)
- E: Subjects requiring hemodialysis (saxagliptin dose administered prior to the day's dialysis session)

On the morning of Day 1, all subjects received a single oral dose of 10 mg saxagliptin under fasting conditions. 40 subjects (27 male; 13 female) were dosed with saxagliptin 10 mg (2 x 5 mg). The ethnic distribution was as follows: White (31) and Black (9). Subjects undergoing hemodialysis had their saxagliptin dose administered 2 h prior to their 4 h hemodialysis session (between 2-6 h post-dosing with saxagliptin). Blood and urine samples were collected for pharmacokinetic (PK) analyses up to 72 h post-dose. Subjects were discharged from the study in the morning of Day 4 after completing the 24-h urine collection and safety evaluation.

Results: The plot of mean plasma concentration-time profiles and the PK parameters of saxagliptin for all subjects are provided in Figure 1 and Table 1 below:

Figure 1: Mean (+ SD) Plasma Concentration-Time Profiles for Saxagliptin in Subjects with Normal Renal Function, Subjects with Mild, Moderate and Severe Renal Impairment and Subjects on Hemodialysis

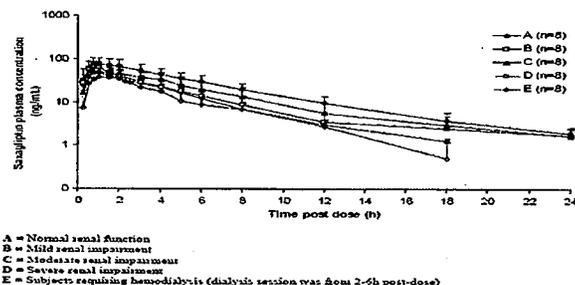


Table 1: PK parameters for saxagliptin

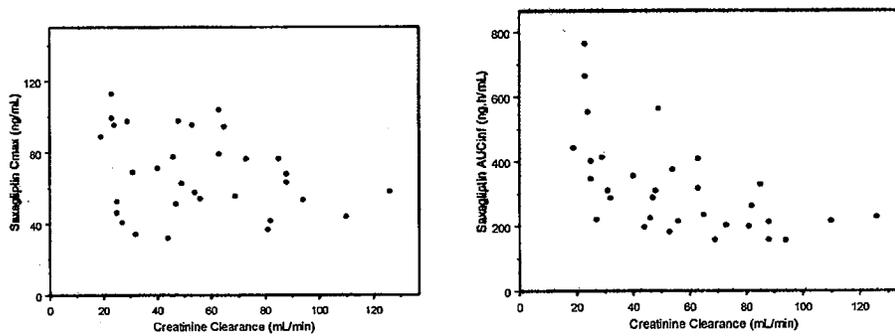
Saxagliptin Pharmacokinetic Parameter	Renal Function Group					
	Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=8)	Severe (n=7*)	Hemodialysis (n=5)
C_{max} (ng/mL)						
Geo. Mean (CV%)	54 (25)	75 (26)	58 (36)	74 (35)	72 (38)	46 (35)
AUC(NF)(ng·h/mL)						
Geo. Mean (CV%)	215 (25)	249 (36)	303 (35)	447 (37)	434 (40)	170 (37)
AUC(0-T)(ng·h/mL)						
Geo. Mean (CV%)	208 (26)	240 (36)	292 (35)	437 (37)	423 (41)	160 (40)
T_{max} (h)						
Median	0.63	0.68	1.50	1.00	1.00	0.33
(Min, Max)	(0.50, 1.50)	(0.25, 1.50)	(0.50, 3.00)	(0.50, 1.50)	(0.50, 1.00)	(0.50, 3.00)
T_{1/2} (h)						
Mean (SD)	3.09 (0.65)	3.50 (1.62)	4.02 (1.23)	4.42 (1.06)	4.41 (1.14)	3.39 (0.21)
CL_{TR} (mL·min)						
Mean (SD)	796 (191)	705 (230)	572 (165)	399 (168)	414 (176)	1039 (353)
%UR or %DR (%)						
Mean (SD)	20 (4)	20 (6)	12 (9)	7 (5)	7 (4)	4 (1)
CL_R (mL·min)						
Mean (SD)	153 (23)	131 (37)	61 (23)	26 (8)	25 (9)	Not applicable
CL_D (mL·min)						
Mean (SD)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	91 (35)

Note: *Subject CV181019-1-26 was receiving rifedipine (CYP3A4 inhibitor) and hence excluded from the analysis. Since saxagliptin is a CYP3A4 substrate, rifedipine may have altered the PK of saxagliptin and the formation of BM5-510849.

%UR: Percent urinary recovery for subjects not on dialysis; %DR: Percent dialysate recovery for subjects on dialysis

Scatter plots of saxagliptin C_{max} and AUC_{inf} versus CL_{CR} are provided below: Saxagliptin C_{max} values were not well correlated with estimated CL_{CR} values. There was clear association between AUC and CrCl, as CL_{CR} values decreased, saxagliptin AUC values generally increased and became more variable.

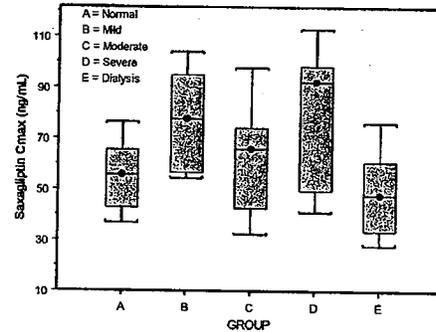
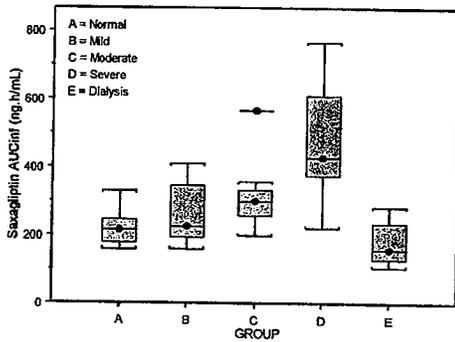
Figure 2: Scatter Plot of plasma Saxagliptin Cmax(left) and AUC (right) versus CLcr



Compared to subjects with normal renal function, subjects with mild, moderate, and Severe renal impairment had:

- 39%, 7%, and 38% higher geometric mean Cmax values of saxagliptin,
- 16%, 41%, and 108% (2.1-fold) higher geometric mean AUCinf values of saxagliptin,
- 15%, 40%, and 110% (2.1-fold) higher geometric mean AUC(0-T) values of saxagliptin

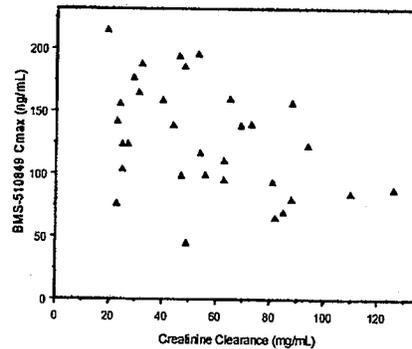
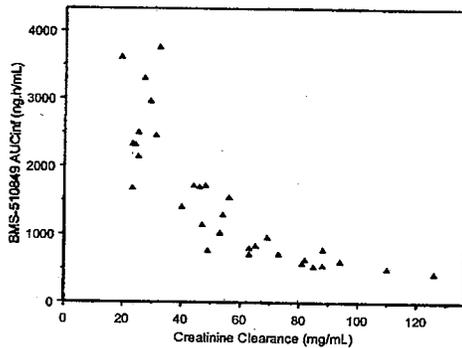
Compared to subjects with normal renal function, subjects on hemodialysis had 15%, 21% and 23% lower geometric mean Cmax, AUC(INF) and AUC(0-T) values of saxagliptin, respectively.



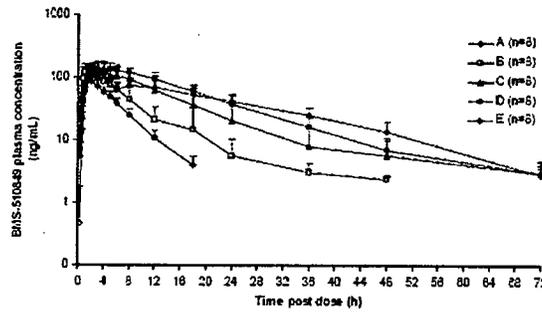
The sponsor has proposed the dose based on renal function:

- No dose adjustment for mild renal impairment
- 2.5 mg for moderate, severe and ESRD patients

BMS-510849 PK results: BMS-510849 plasma Cmax values were not well correlated with estimated CLcr values. As CLcr values decreased, BMS-510849 AUCinf values generally increased.



Mean (+ SD) Plasma Concentration-Time Profiles for BMS-510849 in Subjects with Normal Renal Function, Subjects With Mild, Moderate and Severe Renal Impairment and Subjects on Hemodialysis



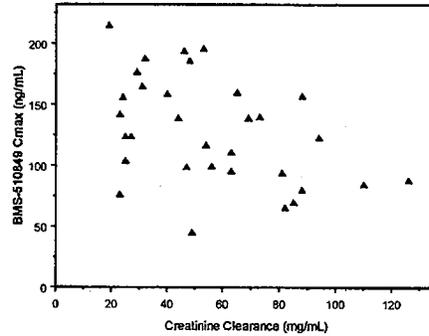
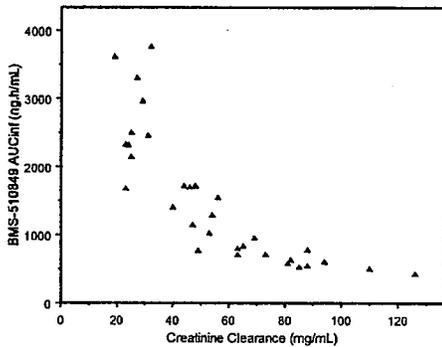
A = Normal renal function
 B = Mild renal impairment
 C = Moderate renal impairment
 D = Severe renal impairment
 E = Subjects requiring hemodialysis (dialysis session was from 2-6h post-dose)

Compared to subjects with normal renal function, subjects with mild, moderate, severe renal function and ESRD had:

- 40%, 47%, 46%, and 36% higher geometric mean C_{max} values of BMS-510849,
- 67%, 192% (2.9-fold), 347% (4.5-fold), and 309% (4.1-fold) higher geometric mean AUC_{inf} values of BMS-510849,
- 67%, 191% (2.9-fold), 347% (4.5-fold), and 306% (4.1-fold) higher geometric mean AUC(0-T) values of BMS-510849.

BMS-510849 Pharmacokinetic Parameter	Renal Function Group					Hemodialy- sis (n=8)
	Normal (n=8)	Mild (n=8)	Moderate (n=8)	Severe (n=7*)		
C _{max} (ng/mL) Geo. Mean (CV%)	92 (32)	129 (26)	135 (35)	134 (31)	131 (34)	125 (37)
AUC _{inf} (ng·h/mL) Geo. Mean (CV%)	569 (18)	950 (30)	1660 (50)	2541 (25)	2574 (26)	2330 (50)
AUC(0-T) (ng·h/mL) Geo. Mean (CV%)	555 (18)	929 (30)	1617 (51)	2479 (25)	2508 (27)	2257 (30)
T _{max} (h) Median (Min, Max)	1.25 (0.92, 2.00)	1.75 (1.00, 3.00)	4.00 (2.00, 8.28)	5.00 (2.00, 8.00)	5.00 (2.00, 8.00)	2.63 (2.00, 4.00)
T _{1/2} (h) Mean (SD)	3.85 (0.56)	5.83 (2.72)	8.55 (2.44)	9.59 (1.43)	9.88 (1.23)	12.51 (1.34)
%UR or %ADR (%) Mean (SD)	27 (7)	19 (4)	25 (6)	20 (5)	19 (5)	19 (4)
CLR (mL/min) Mean (SD)	76 (11)	52 (17)	28 (13)	13 (3)	12 (3)	Not applicable
CLD (mL/min) Mean (SD)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	89 (21)

Note: *Subject CV181019-1-26 was on mifepristone (CYP3A4 inhibitor) and hence excluded from the analysis. Since saxagliptin is a CYP3A4 substrate, mifepristone may have altered the PK of saxagliptin and the formation of BMS-510849.
 %UR: Percent urinary recovery for subjects not on dialysis; %ADR: Percent dialysis recovery for subjects on dialysis.



Saxagliptin and BMS-510849 were cleared by dialysis, with mean (range) extraction efficiencies of approximately 48% (27-59%) and 77% (43-90%), respectively. Although the mean half life of saxagliptin was not substantially different in subjects with various degrees of renal impairment (range 3.1 to 4.4 hours), the half-life for BMS-510849 increased with increasing degree of renal impairment (range of 3.9 to 12.5 hours).

The table below demonstrates that the metabolite levels increase with decreasing renal function.

BMS-510849		
	Metabolite AUC ratio compared to healthy	AUC ratio Metabolite/Parent
Healthy	1.0	2.6
Mild	1.7	3.8
Moderate	3.2	5.8
Severe	4.5	5.5
ESRD	4.2	13.4

Bioanalytical: Analysis of urine and plasma PK samples for measurement of saxagliptin and BMS-510849 were performed by C. Analysis of urine and plasma PK samples for measurement of iohexol was performed by C. The samples (plasma, urine and dialysate) were analyzed for saxagliptin and BMS-510849 with a validated LC/MS/MS method. All samples were analyzed during the period within which their analytes were known to be stable.

Table: Summary of Assay Performance for Saxagliptin, and BMS-510849

Analyte	LLQ (ng/mL)	ULQ (ng/mL)	Between-run %CV*	Within-run %CV*	Mean % Deviation from Nominal Concentration*
Saxagliptin and BMS-510849 in Human Plasma					
Saxagliptin	1.0	100	≤ 6.2	≤ 26.3	± 6.0
BMS-510849	2.0	200	≤ 8.8	≤ 37.5	± 8.8
Saxagliptin and BMS-510849 in Human Urine (Discriminatory assay)					
Saxagliptin	5.0	1250	≤ 7.1	≤ 4.9	± 3.3
BMS-510849	10.0	2500	≤ 8.6	≤ 7.6	± 8.0
Saxagliptin and BMS-510849 in Human Dialysate					
Saxagliptin	1.0	100	Not applicable	Not applicable	± 3.5
BMS-510849	2.0	200	Not applicable	Not applicable	± 5.8

Comments:

- Saxagliptin and BMS-510849 are eliminated in the urine in the amounts of 24% and 36% of administered dose of saxagliptin respectively and therefore it is expected that renal impairment may affect the PK of both the drug and metabolite.
- Subjects were classified into 1 of 4 renal function groups (Groups A-D) according to estimated CL_{Cr} determined by the Cockcroft-Gault calculation using the serum creatinine concentration determined during the screening using the following equation:

CL_{Cr} = [(140-age) x body weight (kg) / (72 x Scr (mg/dL))] x 0.85 (if female), where Scr is the serum creatinine concentration

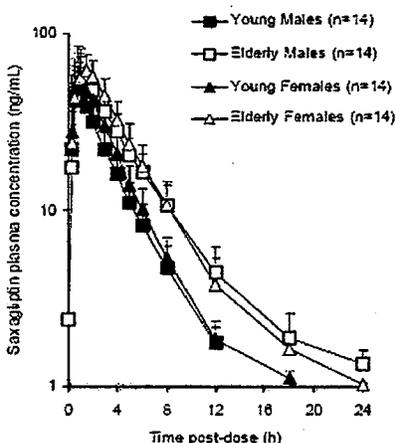
- 32 subjects not receiving dialysis received a single intravenous (IV) dose of 5 mL of 300 mg/mL iohexol, infused at a constant rate into a peripheral vein over 15 minutes for determination of glomerular filtration rate (GFR) using the equation, GFR = dose of iohexol/plasma AUC_{inf}. The iohexol clearance generally correlated with the creatinine clearance calculated using CG equation.
- Additionally, during this visit, measured CL_{Cr} was determined from urinary creatinine excretion (U_{Cr}) over 24 hour (h) and serum creatinine measured at the 12-h time point. Subjects were released from the clinical facility after collection of the 24 h samples and reported back to the study facility on Day -1.
- The dose of saxagliptin tested was 10 mg (2x 5 mg tablets) which is the highest dose studied in the Phase 3 program.
- One subject (1-26) was receiving 30 mg nifedipine (moderate CYP3A4 inhibitor) and this may have altered the PK of saxagliptin. Therefore, sponsor conducted analysis with and without the data for this subject.
- Renal impairment is not expected to alter the plasma protein binding of saxagliptin and BMS-510849 as *in vitro* protein binding of both compounds in human serum was very low. (renal clearance here refers to unbound renal clearance).

Effects of Age and Gender on the Single-Dose Pharmacokinetics of BMS-477118 in Healthy Subjects

Study period: 12 Sept 2005 – 20 Nov 2005

The primary objective was to determine the effects of age and gender on the single-dose pharmacokinetics of saxagliptin. This was an open-label, single-dose, 2x2 factorial design study comparing the single-dose pharmacokinetics of saxagliptin in 4 stratified demographic groups. Fifty-six (56) subjects were divided into the following 4 demographic groups (14 subjects per group): young males (18 - 40 years), elderly males (≥ 65 years), young females (18 - 40 years) and elderly females (≥ 65 years). On Day 1, subjects received a single oral dose of 10 mg (2 x 5 mg) saxagliptin under fasting conditions. Blood and urine samples were collected for pharmacokinetic analyses up to 48 hours post-dose.

Mean (+ SD) Plasma Concentration-Time Profiles for Saxagliptin Following Single Oral 10 mg Doses of Saxagliptin to Healthy Young and Elderly Male and Female Subjects (n=14/group) in Study CV181018



Sponsor pooled the results across the gender and age groups and concluded the following: The geometric means of C_{max} , AUC_{inf} and $AUC(0-T)$ of saxagliptin were, respectively, 14%, 15% and 16% higher in female subjects than in male subjects. The sponsor used a wider 90% CI to compare males and females. The conclusion was made regarding lack of gender effect since the corresponding 90% confidence intervals for the female to male ratios of geometric means were within 0.75, 1.33.

The geometric means of C_{max} , AUC_{inf} and $AUC(0-T)$ of saxagliptin were, respectively, 23%, 59% and 61% higher in elderly than in young subjects. Adjustment for CL_{cr} and body weight reduced the difference to 12%, 29% and 30% for C_{max} , AUC_{inf} and $AUC(0-T)$, respectively. However, the pre-specified 0.75-1.33 criterion for absence of effect was still not met.

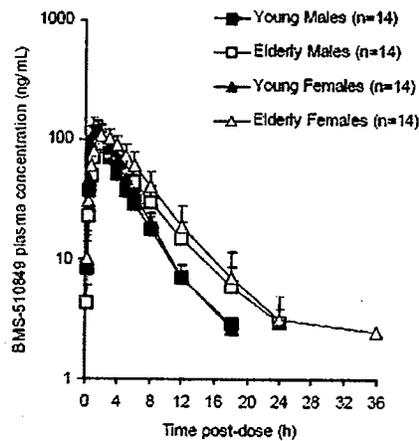
Table: Summary Statistics for Saxagliptin Pharmacokinetic Parameters Body Weight and CLcr By Age/Gender Group

Pharmacokinetic Parameter	Age/Gender Group			
	Young Males (n=14)	Young Females (n=14)	Elderly Males (n=14)	Elderly Females (n=14)
C_{max} (ng/mL)				
Geometric Mean (CV%)	51 (25)	57 (36)	61 (19)	71 (26)
T_{max} (h)				
Median (Min, Max)	0.63 (0.50, 1.50)	0.75 (0.50, 2.00)	1.00 (0.50, 2.00)	1.00 (0.50, 2.00)
AUC_(0-∞) (ng·h/mL)				
Geometric Mean (CV%)	164 (20)	203 (29)	232 (19)	301 (19)
AUC_(0-T) (ng·h/mL)				
Geometric Mean (CV%)	157 (20)	197 (30)	273 (19)	294 (20)
T-1/2 (h)				
Mean (SD)	2.52 (0.41)	2.49 (0.25)	3.26 (0.92)	2.91 (0.50)
CL_TF (mL·min)				
Mean (SD)	1036 (233)	840 (182)	602 (114)	562 (105)
CL_R (mL·min)				
Mean (SD)	199 (39)	183 (37)	142 (31)	127 (30)
%CL_R (%)				
Mean (SD)	20 (5)	23 (6)	24 (5)	23 (5)
V_{st}F (L)				
Mean (SD)	225 (59)	134 (52)	182 (39)	147 (27)
Body Weight (kg)				
Mean (SD)	75 (11)	70 (12)	80 (7)	73 (10)
CL_{cr} (mL·min)				
Mean (SD)	126 (23)	124 (26)	80 (18)	79 (10)

BMS-510489 PK results:

The mean plasma concentration-time profiles are shown and BMS-510849 pharmacokinetic parameters are summarized by age group and gender in figure and table below:

Mean (+ SD) Plasma Concentration-Time Profiles for BMS-510849 Following Single Oral 10 mg Doses of Saxagliptin to Healthy Young and Elderly Male and Female Subjects (n=14/group)



Summary Statistics for BMS-510849 Pharmacokinetic Parameters Body Weight and CLcr By Age/Gender Group

Pharmacokinetic Parameter	Age/Gender Group			
	Young Males (n=14)	Young Females (n=14)	Elderly Males (n=14)	Elderly Females (n=14)
C_{max} (µg/mL)				
Geometric Mean (C.V.%)	102 (29)	121 (25)	90 (34)	118 (21)
T_{max} (h)				
Median (Min, Max)	1.50 (0.75, 2.00)	1.25 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 4.00)
AUC(INF) (ng·h/mL)				
Geometric Mean (C.V.%)	474 (22)	561 (22)	610 (31)	797 (24)
AUC(0-T) (ng·h/mL)				
Geometric Mean (C.V.%)	458 (22)	548 (22)	591 (31)	780 (24)
T_{1/2} (h)				
Mean (S.D.)	3.12 (0.55)	2.93 (0.50)	4.35 (0.63)	4.13 (0.63)
CL_R (mL/min)				
Mean (S.D.)	101 (18)	93 (17)	75 (19)	65 (15)
%CL_R (%)				
Mean (S.D.)	29 (7)	31 (7)	28 (7)	31 (7)
Body Weight (kg)				
Mean (S.D.)	75 (11)	70 (12)	80 (7)	73 (10)
CL_{cr} (mL/min)				
Mean (S.D.)	126 (23)	124 (26)	80 (18)	79 (10)

The geometric means of C_{max}, AUC_{inf} and AUC(0-T) of BMS-510849 were, respectively, 25%, 24% and 26% higher in female subjects than in male subjects, and the corresponding 90% confidence intervals for the female to male ratios of geometric means extended above the (0.75, 1.33) no-effect interval according to the sponsor. Adjusting for CL_{cr} and body weight yielded very similar results.

Although the geometric mean of C_{max} of BMS-510849 was 7% lower in elderly than in young subjects, the 90% confidence interval for the elderly to young ratio of geometric mean was still within the pre-specified no effect criterion of 0.75-1.33 as per sponsor's conclusions. The geometric means of AUC_{inf} and AUC(0-T) of BMS-510849 were, respectively, 35% and 36% higher in elderly than in young subjects, and the pre-specified 0.75-1.33 criterion for absence of effect was not met. Additionally according to the sponsor adjusting for CL_{cr} and body weight reduced the differences and the corresponding 90% confidence intervals satisfied the no-effect criterion for both AUC_{inf} and AUC(0-T) of BMS-510849.

Comments:

- The sponsor concluded an "Absence of effect" of a factor (age group or gender) on C_{max} or AUC_{inf} of saxagliptin since the corresponding 90% confidence interval for the ratio of population geometric means for the two levels of that factor was contained within an equivalence interval from 75% to 133%. The sponsor has stated that since saxagliptin is generally safe and well tolerated, the wide interval was used.
- The elderly patients with GFR of at least 60 mL/min were included.

- Elderly subjects had higher systemic exposures to saxagliptin (approximately 60%) and BMS-510849 (35%) compared to young subjects. Urinary excretion is an important route of elimination for saxagliptin. The mean renal clearance values for saxagliptin (191 and 134 mL/min for young and elderly subjects, respectively) reflected the declining renal function associated with increasing age (mean creatinine clearance of 125 and 79 mL/min for young and elderly subjects, respectively). However, renal function alone does not explain the differences, since the mean amounts of saxagliptin excreted in the urine (21 and 23% of the ingested dose for young and elderly subjects, respectively) were similar between the age groups. Since the majority of saxagliptin that is not cleared renally is likely to be metabolized, the balance of the difference in saxagliptin systemic clearance is probably due to a decreased metabolic capacity (intrinsic clearance and/or reduced hepatic blood flow) with increased age. Interestingly, the mean percentage of the saxagliptin dose recovered as BMS-510849 in the urine was similar between young and elderly subjects (30 and 29 %, respectively) suggesting the overall extent of metabolism of saxagliptin is not substantially different between the age groups. A small proportion of the higher systemic exposure to saxagliptin in elderly compared to young subjects also may have been due to differences in the apparent volume of distribution of saxagliptin between the age groups. The mean V_{ss}/F values in young and elderly subjects were 205 and 164 L, respectively.
- Females had slightly higher systemic exposures to saxagliptin (by 15%) and BMS-510849 (by approximately 25%) males.
- Elderly females had about 39%, 84% and 87% increase in saxagliptin C_{max} , AUC_{inf} and AUC_{0-t} respectively as compared to young males and about 15%, 68% and 70% increase in BMS-510849 C_{max} , AUC_{inf} and AUC_{0-t} respectively.
- Elderly males had about 20%, 72% and 74% increase in saxagliptin C_{max} , AUC_{inf} and AUC_{0-t} respectively as compared to young males and about 20% increase in AUCs of BMS-510849.
- Elderly females had about 25%, 48% and 49% increase in saxagliptin C_{max} , AUC_{inf} and AUC_{0-t} respectively as compared to young females and about 42% increase in BMS-510849 AUCs.

TITLE OF STUDY CV181034: Effect of a High-Fat Meal on the Pharmacokinetics of Saxagliptin in Healthy Subjects

STUDY PERIOD: 16-Oct-2006 - 10-Nov-2006

This was an open-label, randomized, 2-period, 2-treatment, crossover study in healthy subjects. On Day -1, following a 21-day screening period, subjects were admitted to the clinical facility. On Day 1, subjects received either a single oral 10 mg dose of saxagliptin administered in the fasted state (Treatment A) or a single oral 10 mg dose of saxagliptin administered with a high-fat meal (Treatment B) in 1 of 2 randomly assigned

treatment sequences. Approximately 48 hours later (Day 3), subjects were administered the alternate treatment. A total of 14 subjects were randomized and completed study treatment.

These results suggest that there was an effect of a high-fat meal on saxagliptin AUCinf. When administered with a high-fat meal, saxagliptin AUCinf increased by 27%. Although Cmax increased by 7.7% when saxagliptin was administered with a high-fat meal, the 90% confidence intervals for ratios of Cmax geometric means fell within the equivalence interval of 80% to 125%, indicating an absence of effect on Cmax.

Figure: Mean (+ SD) plasma concentration-time profiles for saxagliptin following administration of single oral 10 mg dose of saxagliptin to healthy subjects in the fasted state and after a high-fat meal (n=14)

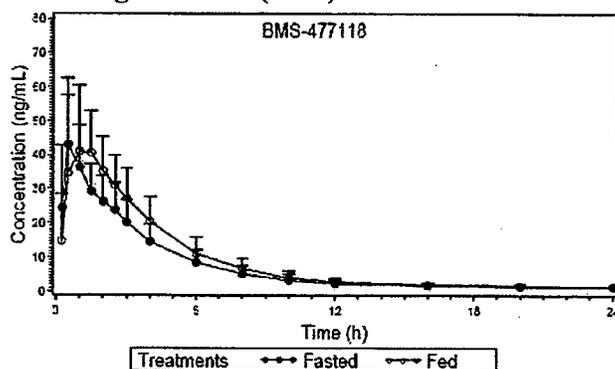


Table: Summary statistics for saxagliptin pharmacokinetic parameters

Pharmacokinetic Parameter	Treatment	
	A (n=14)	B (n=14)
Cmax (ng/mL)		
Geometric Mean (CV %)	46.40 (27)	49.97 (25)
Tmax (h)		
Median (Min, Max)	0.53 (0.23, 2.47)	0.99 (0.50, 4.00)
AUC(0-T) (ng·h/mL)		
Geometric Mean (CV %)	144.30 (56)	184.98 (26)
AUC(INF) (ng·h/mL)		
Geometric Mean (CV %)	150.11 (55)	190.69 (26)
T-HALF (h)		
Mean (SD)	2.91 (0.95)	3.12 (1.17)

Pharmacokinetic Parameter	Adjusted Geometric Means		B/A Ratio of Adjusted Geometric Means	
	A	B	Point Estimate	90% CI
Cmax (ng/mL)	46.40	49.97	1.077	(0.930, 1.246)
AUC(INF) (ng·h/mL)	150.11	190.69	1.270	(1.188, 1.358)

Treatments: A = 10 mg saxagliptin administered in the fasted state

B = 10 mg saxagliptin administered following a high-fat meal

Note: Greater variability in Tmax in presence of food.

BMS-510849: The mean plasma concentration time profiles for BMS-510849 are shown below when administered with and without food.

Figure: Mean (+ SD) plasma concentration-time profiles for BMS-510849 following administration of single oral 10 mg dose of saxagliptin to healthy subjects in the fasted state and after a high-fat meal (n=14)

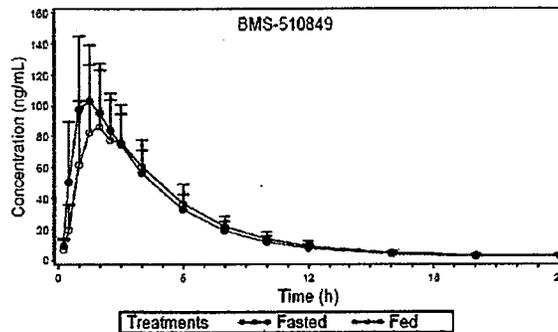


Table: Summary statistics for BMS-510849 pharmacokinetic parameters

Pharmacokinetic Parameter	Treatment			
	A (n=14)	B (n=14)		
Cmax (ng/mL)				
Geometric Mean (CV%)	107.60 (33)	88.23 (37)		
Tmax (h)				
Median (Min, Max)	1.47 (0.97, 2.47)	1.98 (1.47, 4.00)		
AUC(0-T) (ng·h/mL)				
Geometric Mean (CV%)	501.54 (25)	486.11 (27)		
AUC(INF) (ng·h/mL)				
Geometric Mean (CV%)	518.81 (23)	503.08 (26)		
T-HALF (h)				
Mean (SD)	4.56 (1.39)	4.56 (1.25)		
Pharmacokinetic Parameter	Adjusted Geometric Means		B/A Ratio of Adjusted Geometric Means	
	A	B	Point Estimate	90% CI
Cmax (ng/mL)	107.60	88.23	0.820	(0.756, 0.914)
AUC(INF) (ng·h/mL)	518.81	503.08	0.970	(0.919, 1.023)

These results suggest that there was an effect of a high-fat meal on BMS-510849 Cmax. When administered with a high-fat meal, BMS-510849 Cmax decreased by 18%. Although AUCinf decreased by 3% when saxagliptin was administered with a high-fat meal, the 90% confidence intervals for ratios of BMS-510849 AUCinf geometric means fell within the equivalence interval of 80% to 125%, indicating an absence of effect on AUCinf.

Bioanalytical: The concentrations of saxagliptin and BMS-510849 in human plasma were determined using solid phase extraction with subsequent analysis by LC/MS/MS. The Lower Limit of Quantitation (LLOQ) for the analyses of 446 samples was established at 1.00 ng/mL for saxagliptin and 2.00ng/mL for BMS-510849.

Comments:

- This study was conducted with the highest dose (10 mg) that was used in Phase 3 program.
- The formulation used was a [] tablet which is almost identical to the anticipated marketed formulation. This was discussed at the PNDA meeting and it was agreed that the final to-be-marketed formulation was not significantly different to that of the formulation used in the definitive food effect study.
- The median Tmax of saxagliptin was prolonged from 0.53 h to 0.99 h when saxagliptin was administered following a high-fat meal, and can be attributed to an increase in gastric transit time. The median Tmax of BMS-510849 increased from 1.47 h to 1.98 h following a high-fat meal. There was a greater variability in Tmax in presence of food for both parent and metabolite.
- Overall there was a 27% increase in AUC of saxagliptin and a decrease in exposure of metabolite (Cmax decreased by 18%); possible alteration in the metabolism of saxagliptin in presence of a high-fat meal.
- Sponsor is proposing that saxagliptin can be administered either in fasted or fed state.
- Biowaiver request: The sponsor is requesting biowaiver for conducting additional clinical food effect studies with the proposed 2.5 mg and 5 mg tablets and to apply the findings from the 10 mg food effect study to these lower strength tablets. No separate clinical study is required to characterize the effect of food on the lower strength formulations based on:
 - Similarity of composition of 2.5 mg, 5 mg and 10 mg tablets.
 - Saxagliptin can be considered as highly soluble based on the 5 mg tablet strength (and also 10 mg tablet strength).
 - Dissolution profiles of all 3 strengths is rapid and similar in 3 pH (0.1N HCl, 4.5 and 6.8)

b(4)

TITLE OF STUDY: Single-Dose Pharmacokinetics and Safety of 10 mg Saxagliptin in Subjects with Hepatic Impairment Compared to Healthy Adult Subjects

STUDY PERIOD: 28-Mar-2006 - 18-May-2007

This was an open-label, parallel group, single-dose study in 18 hepatically-impaired and 18 healthy subjects (6 in each Child-Pugh class A, B or C). 36 subjects were treated with

a single dose of saxagliptin 10 mg (2 x 5 mg tablets) under fasting conditions. Thirty-five (35) subjects were white and 1 was black. The mean age was 52 years (range 40-58 years) and mean body mass index was 27.5 kg/m² (range 19.0-33.9 kg/m²). Serial blood and urine samples were collected up to 48 h post-dose.

Summary statistics for saxagliptin PK parameters by hepatic function group and subject status

Hepatic Function Group	Subject Status	Saxagliptin Pharmacokinetic Parameters				
		C _{max} (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	T _{max} (h) Median (Min, Max)	T _{1/2} (h) Mean (SD)
A (Mild)	Impaired (n = 6)	60.4 (17)	216 (26)	210 (26)	1.00 (0.50, 1.50)	2.74 (0.27)
	Healthy (n = 6)	56.14 (35)	197 (18)	192 (18)	1.00 (0.50, 1.00)	2.77 (0.35)
B (Moderate)	Impaired (n = 6)	77.1 (40)	286 (53)	278 (53)	1.00 (0.50, 2.00)	3.54 (1.14)
	Healthy (n = 6)	75.9 (33)	207 (25)	201 (23)	0.50 (0.25, 2.50)	2.82 (0.61)
C (Severe)	Impaired (n = 6)	50.4 (32)	336 (48)	319 (46)	0.75 (0.25, 2.00)	7.27 (3.76)
	Healthy (n = 6)	53.5 (43)	191 (21)	186 (22)	0.50 (0.50, 2.00)	3.10 (0.62)

For the mild hepatic function group, the geometric means for saxagliptin C_{max}, AUC(INF) and AUC(0-T) for impaired subjects were 8%, 10% and 10% higher, respectively, compared to matching healthy subjects. Saxagliptin C_{max}, AUC(INF) and AUC(0-T) geometric means were 2%, 38% and 38% higher, respectively, for moderately impaired subjects compared to matching healthy subjects. For subjects with severe hepatic impairment, compared to matching healthy subjects, geometric mean C_{max} was 6% lower and geometric mean AUC(INF) and AUC(0-T) was 77% and 72% higher, respectively.

Results of Statistical Analyses of Saxagliptin C_{max}, AUC(INF) and AUC(0-T)

Hepatic Function Group	Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
		Subject Status	Mean	Ratio	Point Estimate	90% Confidence Limits
A (Mild)	C _{max} (ng/mL)	Impaired	60	Impaired/Healthy	1.077	(0.763, 1.519)
		Healthy	56			
	AUC(INF) (ng ² h/mL)	Impaired	216	Impaired/Healthy	1.097	(0.828, 1.453)
B (Moderate)	C _{max} (ng/mL)	Impaired	77	Impaired/Healthy	1.016	(0.720, 1.432)
		Healthy	76			
	AUC(INF) (ng ² h/mL)	Impaired	286	Impaired/Healthy	1.383	(1.044, 1.832)
C (Severe)	C _{max} (ng/mL)	Impaired	50	Impaired/Healthy	0.941	(0.667, 1.328)
		Healthy	54			
	AUC(INF) (ng ² h/mL)	Impaired	338	Impaired/Healthy	1.707	(1.334, 2.341)
C (Severe)	C _{max} (ng/mL)	Impaired	319	Impaired/Healthy	1.718	(1.303, 2.268)
		Healthy	186			

Summary statistics for BMS-510849 PK parameters by hepatic function group and subject status

Hepatic Function Group	Subject Status	BMS-510849 Pharmacokinetic Parameters				
		C _{max} (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng ² h/mL) Geom. Mean (CV%)	AUC(0-T) (ng ² h/mL) Geom. Mean (CV%)	T _{max} (h) Median (Min, Max)	T _{1/2} (h) Mean (SD)
A (Mild)	Impaired (n=6)	84.7 (31)	472 (29)	459 (29)	1.58 (1.00, 3.00)	3.52 (0.57)
	Healthy (n=6)	103.4 (28)	602 (11)	578 (12)	1.50 (1.50, 3.00)	4.17 (1.34)
B (Moderate)	Impaired (n=6)	94.1 (31)	500 (42)	482 (43)	1.75 (1.00, 2.00)	4.03 (1.13)
	Healthy (n=6)	111.6 (23)	540 (27)	522 (28)	1.00 (1.00, 2.50)	3.53 (0.90)
C (Severe)	Impaired (n=6)	55.3 (29)	335 (69)	310 (71)	2.25 (1.00, 3.00)	5.71 (2.58)
	Healthy (n=6)	86.2 (33)	500 (28)	484 (28)	1.50 (1.00, 2.50)	3.53 (0.48)

In general, all the PK parameters for hepatic impaired subjects were decreased compared to healthy subjects, in all the hepatic function groups. For the mild hepatic group, geometric mean BMS-510849 C_{max}, AUC(INF), and AUC(0-T) for impaired subjects was decreased by 18%, 22% and 21%, respectively, as compared to matching healthy subjects. Geometric mean BMS-510849 C_{max}, AUC(INF) and AUC(0-T) was decreased by 16%, 7% and 8%, respectively, for moderately impaired subjects compared to matching healthy subjects. For subjects with severe hepatic impairment, compared to

matching healthy subjects, geometric mean BMS-510849 Cmax, AUC(INF) and AUC(0-T) was reduced by 59%, 33% and 36%, respectively.

Analytical:

Table 11.1.1A: Summary of assay and performance for saxagliptin and BMS-510849 in human plasma

Analyte	LLQ (ng/mL)	ULQ (ng/mL)	Between-run %CV*	Within-run %CV*	Mean % Deviation from Nominal Concentration*
Saxagliptin	1.0	100	≤ 5.2	≤ 5.8	± 4.2
BMS-510849	2.0	200	≤ 5.6	≤ 8.6	± 4.0

Table 11.1.1B: Summary of assay and performance for saxagliptin and BMS-510849 in human urine

Analyte	LLQ (ng/mL)	ULQ (ng/mL)	Between-run %CV*	Within-run %CV*	Mean % Deviation from Nominal Concentration*
Saxagliptin	5.0	1250	≤ 3.6	≤ 1.8	± 10.0
BMS-510849	10.0	2500	≤ 19.0	≤ 5.3	± 5.0

Subsequent to the determination of plasma and urine concentrations of BMS-510849, it was found that the employed bioanalytical method overestimated the concentrations of BMS-510849. Consequently, a new bioanalytical method was developed to more accurately quantitate concentrations of BMS-510849 in plasma and urine (refer to study addendum 01 for further details regarding a comparison of the original and new methods).

Comments:

- While hepatically impaired subjects were enrolled into the study based on Child-Pugh class, a 1 mg/kg intravenous dose of lidocaine was administered prior to the start of the study for post-hoc analysis of liver drug metabolizing capacity. The formation of monoethylglycinexylidide (MEGX), a metabolite of lidocaine catalyzed by CYP3A, was used to distinguish differences in metabolic capacity between Child-Pugh classes A, B and C.
- Saxagliptin is predominantly metabolized in the liver by CYP3A and the exposure is expected to increase in hepatic impairment.
- Compared to matched healthy subjects, there was a trend towards higher AUC values for parent and lower AUC values for BMS-510849 with increasing severity of hepatic impairment, indicating a reduced capacity to metabolize saxagliptin as hepatic function declines.
- There was no correlation with smoking status.