

Title of study CV181010: Placebo-controlled, ascending multiple-dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of higher doses of saxagliptin (BMS-477118) in healthy subjects.

Study period: 25-Aug-2003 - 01-May-2004

Method: This was a placebo-controlled, randomized, double-blind, sequential, multiple ascending dose study. 50 subjects were randomized to receive either 40, 100, 150, 200, 300, or 400 mg saxagliptin or matching placebo. Forty (40) subjects received saxagliptin (10 subjects at the 40 mg dose level and 6 subjects per every other dose level) and 10 subjects received placebo. All doses were administered 1 hour prior to breakfast.

Bioanalytical:

Plasma assay for saxagliptin: The standard curves were well fitted by a 1/x-weighted quadratic equation over the concentration range of 5.00 to 1000 ng/mL. Values for the between-run and within-run precision for analytical quality control samples were no greater than 6.4% coefficient of variation (CV), with deviations from the nominal concentrations of no more than $\pm 3.5\%$.

Plasma assay for BMS-510849: The standard curves were well fitted by a 1/x-weighted quadratic equation over the concentration range of 10.0 to 2000 ng/mL. Values for the between-run and within-run precision for analytical quality control samples were no greater than 6.3% CV, with deviations from the nominal concentrations of no more than $\pm 3.7\%$.

Results:

The mean plasma –time concentration profiles are shown in the Figure and the summary of PK parameters are shown in the Table 1. As seen, the PK profiles on Day 1 and Day 14 was similar. There is no evidence of accumulation following once daily dosing for 2 weeks. There is 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 suggested that saxagliptin was at steady-state by Day 4.

Figure 1: Mean (+ SD) Plasma Concentration-Time Profiles for Saxagliptin on Days 1 and 14

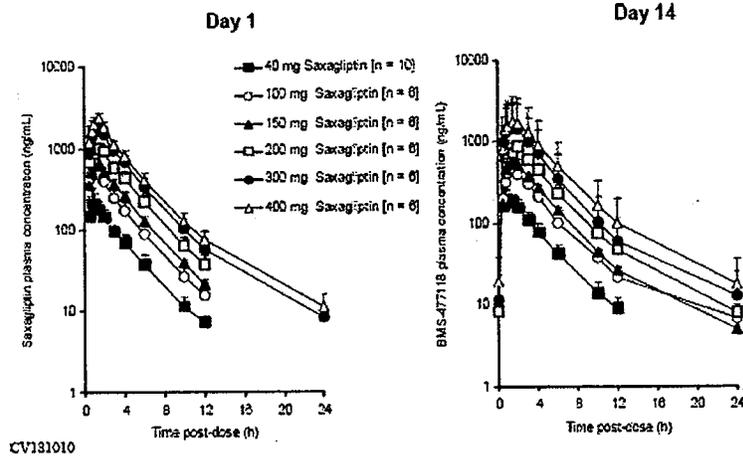


Table 1: Summary Statistics for Saxagliptin PK Parameters

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	2307 (11)	985 (22)
	300 mg	1845 (10)	1640 (31)
	400 mg	2321 (18)	1567 (22)
AUC ₍₀₋₂₄₎ (ng·h/mL) Geometric Mean (C.V. %)	40 mg	739 (25)	800 (24)
	100 mg	1299 (18)	1991 (11)
	150 mg	2543 (11)	2532 (9)
	200 mg	4186 (15)	4090 (10)
	300 mg	6652 (22)	6519 (20)
	400 mg	6264 (14)	6533 (13)
A _i for AUC ₍₀₋₂₄₎ Geometric Mean (C.V. %)	40 mg		1.03 (18)
	100 mg		1.05 (15)
	150 mg		1.00 (15)
	200 mg	N/A	0.99 (19)
	300 mg		0.98 (14)
	400 mg		1.02 (8)
T _{max} (h) Median (Q1, Max)	40 mg	1.60 (0.75, 2.00)	0.88 (0.50, 1.00)
	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} -HALF (h) Mean (S.D.)	40 mg	2.29 (0.15)	2.46 (0.25)
	100 mg	2.82 (0.22)	3.03 (1.20)
	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	5.79 (1.11)	5.48 (2.55)

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 _{TR} 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 (6)
	300 mg	25 (8)	26 (8)
	400 mg	27 (10)	20 (10)
CLR (mL/min) Mean (S.D.)	40 mg	239 (77)	220 (78)
	100 mg	183 (56)	221 (90)
	150 mg	169 (54)	230 (62)
	200 mg	199 (69)	241 (36)
	300 mg	191 (68)	196 (37)
	400 mg	213 (80)	159 (91)

Dose Proportionality: Dose proportionality was estimated using the power model, $(Y = \alpha \cdot Dose^\beta)$ where Y , α and β correspond to the PK parameter (AUC or C_{max}),

proportionality constant and an exponent, respectively), using data from the multiple dose study. If the 90% CI for the slope β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional.

Linear regressions of $\log[C_{max}]$ on $\log(\text{dose})$ and of $\log[AUC]$ on $\log(\text{dose})$ were estimated for saxagliptin and BMS-510849, using the power model described by Gough et al. A slope of 1 would indicate perfect dose proportionality. Point estimates and 90% confidence intervals for the dose-proportionality parameter (slope of the linear regression) were calculated and are shown below:

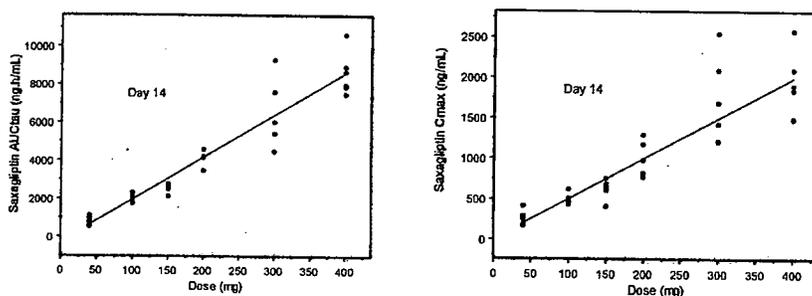
C_{max} Day 1: 1.00 [0.84 – 1.17]

C_{max} Day 14: 0.95 [0.755 – 1.14]

AUC Day 1: 1.06 [0.93 – 1.20]

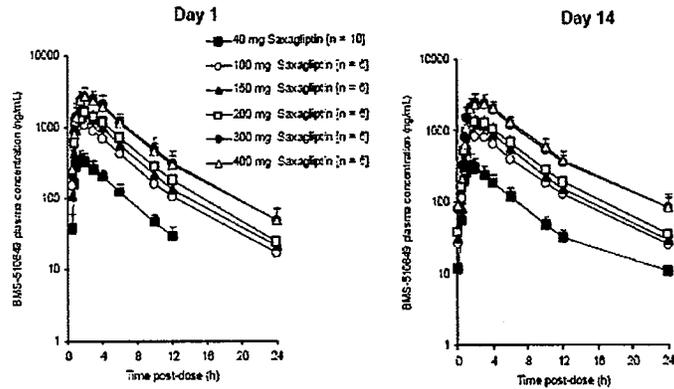
AUC Day 14: 1.03 [0.87 – 1.18]

As the 90% CI for the slope β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional for saxagliptin.



BMS-510849: The mean plasma – time concentration profiles are shown in the Figure and the summary of PK parameters are shown in the Table below.

Figure: Mean (+ SD) Plasma Concentration-Time Profiles for BMS-510849 on Days 1 and 14 Following Once- Daily Oral Doses of Saxagliptin .



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. BMS-510849 trough concentrations suggested that BMS-510849 was at steady-state by Day 4. Mean BMS-510849 urinary recoveries was 21 and 33% of the saxagliptin dose over a dose interval.

Table: Summary Statistics for BMS-510849 PK Parameters

BMS-510849 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)
C _{max} (ng/mL) Geometric Mean (C.V. %)	40 mg	331 (33)	314 (40)
	100 mg	1125 (22)	919 (14)
	150 mg	1550 (10)	1268 (15)
	200 mg	1601 (24)	1389 (24)
	300 mg	2622 (30)	2433 (30)
	400 mg	2649 (18)	2400 (13)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	40 mg	1759 (25)	1705 (30)
	100 mg	6092 (15)	5741 (14)
	150 mg	7992 (13)	7474 (12)
	200 mg	9479 (18)	8850 (22)
	300 mg	15483 (33)	16027 (32)
	400 mg	15357 (18)	16921 (12)
A.I. for AUC(TAU) Geometric Mean (C.V. %)	40 mg		0.98 (15)
	100 mg		0.94 (11)
	150 mg		0.94 (5)
	200 mg	N/A	0.92 (6)
	300 mg		1.04 (11)
	400 mg		1.10 (10)
Molar Ratio for AUC(TAU) ^b Geometric Mean (C.V. %)	40 mg	2.20 (39)	2.00 (47)
	100 mg	3.60 (19)	2.68 (17)
	150 mg	2.94 (21)	2.76 (21)
	200 mg	2.12 (31)	2.02 (30)
	300 mg	2.17 (36)	2.29 (41)
	400 mg	1.72 (22)	1.85 (21)
T _{1/2} (h) Median (Min, Max)	40 mg	1.50 (1.50, 3.00)	1.50 (1.50, 2.00)
	100 mg	1.75 (1.00; 2.00)	1.50 (1.50, 3.00)
	150 mg	2.00 (1.50, 3.00)	2.00 (1.50, 3.00)
	200 mg	2.00 (1.50, 3.00)	2.00 (1.00, 3.00)
	300 mg	2.00 (1.50, 3.00)	2.50 (1.50, 3.00)
	400 mg	2.00 (2.00, 2.00)	2.50 (2.00, 3.00)

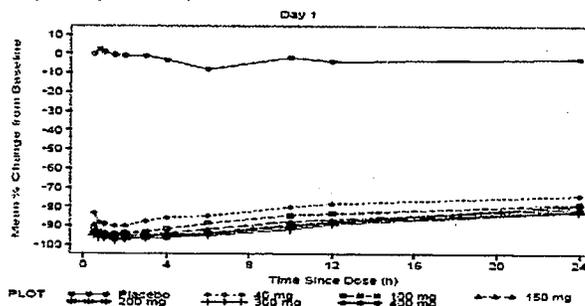
BMS-510849 PK Parameter	Saxagliptin Dose	Study Day	
		Day 1 (n=10 for 40 mg) (n=6 for all other doses)	Day 14 (n=10 for 40 mg) (n=6 for all other doses) ^a
		T-1/2 ^b (h)	40 mg
Mean (S.D.)	100 mg	4.44 (0.31)	5.66 (1.85)
	150 mg	4.19 (0.54)	5.84 (1.96)
	200 mg	4.68 (0.14)	5.98 (1.85)
	300 mg	4.27 (0.32)	7.34 (2.03)
	400 mg	4.41 (0.55)	7.38 (1.71)
%AUC	40 mg	32 (16)	26 (10)
	100 mg	29 (9)	33 (8)
	150 mg	30 (10)	33 (12)
	200 mg	25 (9)	30 (4)
	300 mg	31 (12)	28 (10)
CLR (mL/min)	40 mg	130 (39)	110 (36)
	100 mg	83 (22)	100 (27)
	150 mg	94 (30)	111 (42)
	200 mg	89 (32)	114 (25)
	300 mg	99 (34)	82 (24)
400 mg	113 (35)	79 (41)	

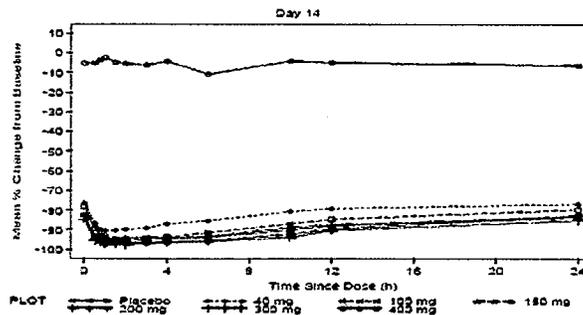
^a n=5 for 200 mg

^b molar ratio = (Metabolite AUC/Parent AUC)*(455.55/487.55)

Plasma DPP-4 Activity: Plasma DPP-4 activity remained constant over the 24 hour observation period in the subjects who received placebo. For subjects who received saxagliptin, 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 T_{max} values for saxagliptin and BMS-510849.

Figure: Plot of Mean Percent Changes from Baseline for Plasma DPP-4 Activity on Day 1 (top) and Day 14 (bottom):





Plasma GLP-1 Levels: In general, dosing with saxagliptin (in the dose ranges of 40 to 200 mg) 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.

Other PD parameters: No apparent dose-dependent effects were observed for glycemic indices or lipid parameters studied in subjects who received saxagliptin in this study. A small saxagliptin dose-dependent decrease was observed in AUC(0-3h) values for plasma glucose after breakfast on Day 8 and 13 compared to baseline. No saxagliptin dose, saxagliptin treatment, or time effect was observed in AUC(0-3h) for serum insulin, serum C-peptide, or the HOMA insulin resistance index were observed on Days 8 or 13 compared to baseline.

Note: The lack of a clear saxagliptin dose, saxagliptin treatment, or time effect on these indices of glycemic control despite robust plasma DPP-IV activity inhibition and increases in active GLP-1 plasma concentrations may have been due to a number of factors such as, but not restricted to: the limited length of the study (2 weeks) may not have been long enough to observe an effect with this mechanism; the study was conducted in healthy subjects who did not have poor glycemic control; confinement of the subject to the clinical facility on a controlled diet; or high within-subject and between-subject variability in the analytes measured.

Comments:

- 1 subject (CV181010-1-30; 25 yr white male) was discontinued from the study due to an AE of mild rash (possible related to study drug) after receiving 200 mg saxagliptin for 9 days.
- Most common AE was pain in extremities (n=3). There were no dose-related trends.
- As the 90% CI for the slope β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional for saxagliptin.
- Within each dose group, the molar AUC ratio of BMS-510849 to saxagliptin did not appear to be different between Days 1 and 14. The apparent terminal-phase half-life values for both saxagliptin and BMS-510849 appeared to be slightly higher (2-3 h more) on Day 14 compared to Day 1. Thus, saxagliptin does not

seem to display time dependent PK when administered once daily to healthy subjects for 2 weeks at doses up to 400 mg, suggesting saxagliptin does not induce or inhibit its own metabolism over time.

- 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.

Title of study CV181002: Placebo-controlled, ascending multiple-dose study to evaluate the safety,

Pharmacokinetics and pharmacodynamics of Saxagliptin in diabetic subjects

Study period: 25-Feb-2002 - 07-Jun-2002

Method: This was a placebo-controlled, randomized, double-blind, sequential, ascending multiple dose designed study. The original protocol stated that subjects were to be assigned to 4 sequential panels (5, 15, 30 or 50 mg BMS-477118 or matched placebo). Based on the preliminary PD data from Study CV181001, the protocol was amended to evaluate lower doses (2.5 mg and 1 mg). However, the 1 mg dose was never evaluated. The 2.5 mg dose was administered as solution (1 mg/mL) while the other doses were administered as capsules. Subjects taking antidiabetic medications at screening were to have a ≥ 7 day washout period. Subjects taking sulfonylureas were to have a 14 day washout period. Drug was administered ~ 5 min after breakfast.

The primary objective of this study was to assess the safety and tolerability of BMS-477118 following oral doses (2.5, 5, 15, 30 and 50 mg) administered once daily for 14 days in subjects with Type 2 diabetes mellitus (T2DM). Effects of saxagliptin on DPP-4 inhibition, glucagon-like peptide-1 (GLP-1), plasma glucose, serum insulin, homeostasis assessment model (HOMA), lipids (LDL, VLDL, HDL triglycerides and total cholesterol) and serum C-peptide was also assessed.

The PK profile of saxagliptin appeared to be similar for Days 1, 7 and 14 and there was no accumulation. The apparent terminal elimination half life appeared to be similar up to 50 mg dose in T2DM patients.

Figure: Mean (plus SD) plasma concentration-time profiles for BMS-477118 on days 1, 7, and 14 following daily dosing administration of 2.5 to 50 mg doses of BMS-477118 to type 2 diabetic subjects in study CV181002

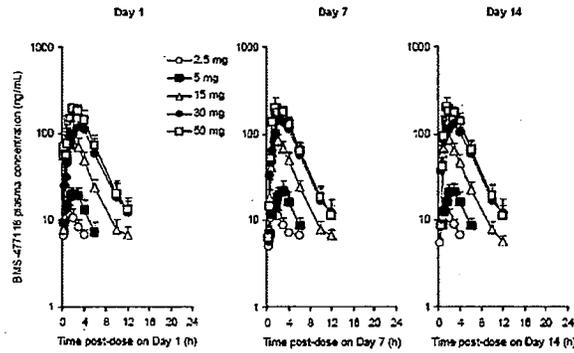
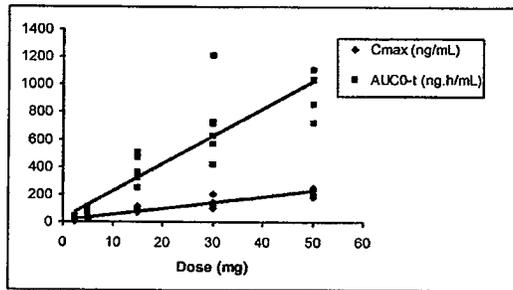


Table 1: Summary Statistics for BMS-477118 Pharmacokinetic Parameters

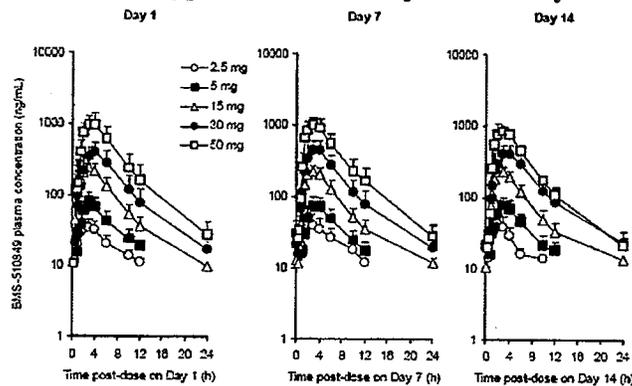
Pharmacokinetic Parameter	BMS-477118 Dose	Study Day		
		Day 1 (n=6)	Day 7 (n=6)	Day 14 (n=6)
C_{max} (ng/mL)	2.5 mg	11 (34)	11 (27)	12 (23)
Geometric Mean (C.V. %)	5 mg	21 ^a (19)	23 (31)	23 (22)
	15 mg	94 (20)	87 (14)	89 (20)
	30 mg	122 (33)	141 (34)	141 (25)
	50 mg	206 (11)	211 (24)	213 ^a (13)
AUC(0-t) (ng·h/mL)	2.5 mg	35 (28)	34 (20)	34 (20)
Geometric Mean (C.V. %)	5 mg	77 ^a (23)	76 (18)	81 (20)
	15 mg	371 (19)	375 (18)	365 (25)
	30 mg	618 (40)	682 (42)	676 (38)
	50 mg	929 (17)	917 (14)	915 ^a (19)
A.I. for AUC(0-t)	2.5 mg		1.05 (16)	1.05 (12)
Geometric Mean (C.V. %)	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 (9)
	50 mg		0.97 (8)	1.04 ^b (2)
T_{max} (h)	2.5 mg	1.50 (0.75, 2.00)	1.25 (1.00, 4.00)	1.50 (0.75, 2.00)
Median (Min, Max)	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)	2.5 mg	3.94 ^a (1.72)	3.67 ^a (1.43)	3.32 (1.11)
Mean (S.D.)	5 mg	2.21 ^a (0.15)	2.25 (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)	2.56 (0.35)
	50 mg	2.17 (0.27)	2.39 (0.34)	2.27 ^b (0.20)
%UR	2.5 mg	14 (7)	14 (3)	12 (4)
Mean (S.D.)	5 mg	12 ^a (7)	22 ^a (7)	13 (5)
	15 mg	22 (4)	21 (5)	22 (5)
	30 mg	25 (6)	24 (4)	15 (3)
	50 mg	18 (4)	14 (7)	12 ^b (5)
CLR (mL/min)	2.5 mg	--	--	--
Mean (S.D.)	5 mg	--	--	--
	15 mg	140 ^c (50)	149 ^c (47)	123 ^b (33)
	30 mg	196 ^a (57)	163 ^a (36)	175 ^a (40)
	50 mg	157 ^a (35)	124 (59)	116 ^b (70)

Figure: Saxagliptin AUC0-t and C_{max} on Day 14 in T2DM patients



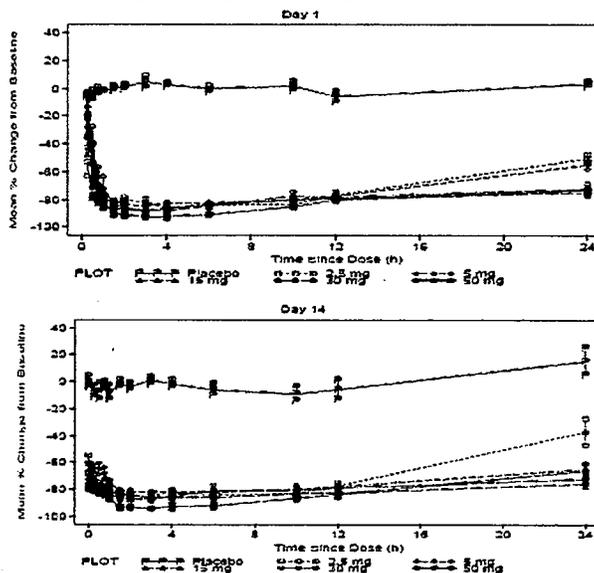
BMS-510849: The mean plasma concentration – time profiles for the metabolite following various doses of saxagliptin is shown below. As seen, there appeared to be no difference in the profiles on Days 1, 7, and 14. The molar ratio of metabolite:parent was similar on Days 1, 7, and 14 within each dose. 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.

Figure: Mean (plus SD) Plasma Concentration-Time Profiles for BMS-510849 on Days 1, 7, and 14 Following Daily Dosing Administration of 2.5 to 50 mg Doses of BMS-477118 to Type II Diabetic Subjects in Study CV181002



Plasma DPP-4 activity: Mean percent changes from baseline for plasma DPP-4 activity values are plotted over 24 h since dosing on Days 1 and 14 by treatment. Dosing with saxagliptin appeared to have a dose-dependent and time-dependent effect on plasma DPP-IV activity. As expected, DPP-IV inhibition was negligible for subjects receiving placebo. For subjects receiving saxagliptin, DPP-IV 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: Plot of Mean Percent Changes from Baseline for Plasma DPP-IV Activity on Day 1 (Top) and Day 14 (bottom)



Plasma active GLP-1 concentrations: Dosing with saxagliptin did not appear to have a dose-dependent or time-dependent effect on plasma active GLP-1 concentrations. For subjects 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.

Bioanalytical: Saxagliptin: Plasma samples were assayed using a MS/MS method. The values for within-run and between run precision (%CV) for quality control samples were < 4.8%. The standard curve was linear in the 5 – 1000 ng/mL range. For urine samples the assay was linear in the range of 25-5000 ng/mL. Values for the between-run and within-run precision for analytical quality control samples were no greater than 3.6% (%C.V.). The metabolite standard curve and QC data also indicate that the plasma and urine assay method was adequate.

Comments:

- T2DM patients were enrolled who had established diagnosis for < 10 years and who were treated with either diet or drugs (insulin, sulfonylureas or acarbose only). HbA1c was in the range of 6.5 -9.5%.

- Dose-proportionality was examined using the power model for saxagliptin AUC and Cmax. Dose proportionality was demonstrated on all days. The results slope (90%CI) for Ln Dose Vs. Ln (AUC/Cmax) are as follows:
 - Cmax Day 14: 0.976 (0.79 – 1.15)
 - AUC Day 14: 1.13 (0.87 – 1.39)
 - Cmax Day 1: 0.98 (0.71 – 1.25)
 - AUC Day 1: 1.14 (0.9 – 1.39)
 - Cmax Day 7: 0.99 (0.82 – 1.16)
 - AUC Day 7: 1.15 (0.86 – 1.43)
- The between subject variability in the molar ratio (metabolite: parent) was relatively large, ranging from 18 to 47% C.V. *In vitro* studies suggest CYP3A 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 CYP3A activity.

Protocol No.: CV181022

Study Date: 06-Oct-2004 – 25-Oct-2004

Title: A study to assess the effects of ketoconazole and BMS-477118 on lymphocyte count in healthy subjects

This was an open-label, randomized, three-sequence study in 36 healthy subjects. After 10-hour fast, subjects were randomized to one of the following 3 sequences:

1=5 mg saxagliptin on Days 1 and 9

2=20 mg saxagliptin on Days 1 and 9

3=20 mg saxagliptin on Day 1, followed by 200 mg ketoconazole q12h on Days 3-8, followed by 200 mg ketoconazole q12h + 20 mg saxagliptin on Day 9

The subjects were maintained in a fasted state for 4 h post-dose after saxagliptin administration. Ketoconazole was given following breakfast and dinner on Days 3-8. PK of saxagliptin and BMS-510849 was measured after Day 1 and Day 9 up to 48 h post-dose and trough samples were measured for ketoconazole on Days 7, 8, and 9 pre-dose.

To determine the effects of the treatments administered on Day 9 on the changes in absolute lymphocyte counts (ALC), an analysis of variance was performed on Day 9 %ΔALC, where

$$\% \Delta \text{ALC} = \left[\frac{\text{lowest recorded ALC on Day 9}}{\text{ALC at corresponding time on Day 8}} - 1 \right] \times 100\%$$

The mean (SD) plasma saxagliptin concentration versus time profile following a single dose of saxagliptin on Days 1 and 9 and with 200 mg ketoconazole q 12 h is shown below. When 20 mg saxagliptin was co-administered with 200 mg ketoconazole q12h, the geometric means for Cmax, AUCinf, and AUC(0-T) of saxagliptin increased by 144%, 267%, and 279%, respectively, relative to those observed following administration of 20 mg saxagliptin alone.

Correspondingly, a decrease in BMS-510849 plasma level was observed when 20 mg saxagliptin was co-administered with 200 mg ketoconazole q 12 h. Subjects CV181022-1-18, CV181022-1-19 and CV181022-1-22 did not receive a second dose of saxagliptin on Day 9 and were therefore not included in the summary statistics. Additionally, eight (8) of the eleven (11) subjects who were administered ketoconazole on Day 9 did not have sufficient quantifiable BMS-510819 plasma (LLQ = 10 ng/mL) levels to calculate the PK parameters and were not included in the summary statistics. Statistical analyses were not performed on Cmax, AUC(INF), and AUC(0-T) of BMS-510849, since only 3 subjects have pharmacokinetic data of BMS-510849 on both Days 1 and 9 (see figure below).

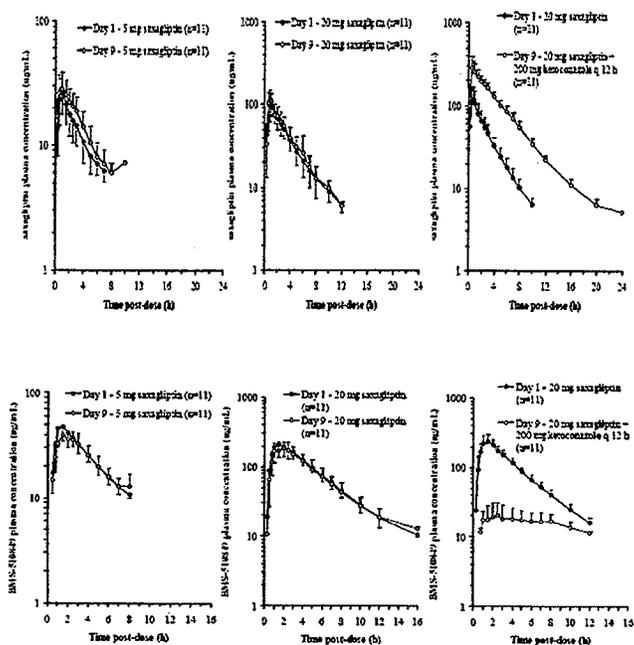


Table 2: Results of Statistical Analyses on Saxagliptin Cmax, AUC(INF) and AUC(0-T)

Pharmacokinetic Parameter	Geometric Means		Ratio of Geometric Means (Day 9: Day 1)	
	Day 1	Day 9	Point Estimate	90% C.I
Cmax (ng/mL)	126	306	2.44	(2.03, 2.95)
AUC(INF) (ng/mL·h)	371	1360	3.67	(3.30, 4.08)
AUC(0-T) (ng/mL·h)	349	1322	3.79	(3.39, 4.24)

Days: 1 = 20 mg saxagliptin

9 = 20 mg saxagliptin + 200 mg ketoconazole q12h

Absolute lymphocyte count:

Table below shows the mean ± SD values for absolute lymphocyte count by sequence, study day, and time point.

Following administration of a single 5 or 20 mg dose of saxagliptin one week earlier, administration of a second single dose of 5 or 20 mg saxagliptin did not result in a ≥ 30 % decrease in absolute lymphocyte counts. 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 in all sequences. The sponsor claims that this change was not associated with any clinical signs or symptoms.

Sequence	Absolute Lymphocyte Count, Mean ± SD (x 10 ⁹ c/mL)										
	Day 8					Day 9				Day 11	Day 12
	0 h	4 h	10 h	16 h	24 h	4 h	10 h	16 h	24 h	0 h	0 h
1	2.22 ± 0.55	2.04 ± 0.43	2.45 ± 0.59	2.72 ± 0.75	2.26 ± 0.45	2.07 ± 0.52	2.32 ± 0.45	2.44 ± 0.55	1.82 ± 0.31	1.89 ± 0.48	2.13 ± 0.43
2	2.18 ± 0.54	2.00 ± 0.53	2.29 ± 0.60	2.51 ± 0.59	2.08 ± 0.44	1.88 ± 0.49	2.02 ± 0.53	2.20 ± 0.68	1.65 ± 0.44	1.79 ± 0.50	1.99 ± 0.54
3	2.06 ± 0.36	1.95 ± 0.37	2.69 ± 0.40	2.49 ± 0.56	1.87 ± 0.31	1.56 ± 0.55	1.82 ± 0.62	1.87 ± 0.82	1.35 ± 0.42	1.07 ± 0.31	1.88 ± 0.49

The present study was powered to detect a decrease of ALC of greater than 30% (%ΔALC). If the point estimate and/or the 90% confidence interval for %ΔALC on Day 9 was less than -30%, then a decrease in ALC would be concluded. A decrease in ALC was only observed in Sequence 3 (200mg ketoconazole q12h co-administered with 20 mg saxagliptin). In sequence 3 (200mg ketoconazole q12h co-administered with 20 mg saxagliptin) both the point estimate of %ΔALC (-30.6%) and the lower 90% confidence bound (-36.9%) on Day 9 fell below the pre-specified -30% %ΔALC level. The

Table 12.8.4B: Results of Statistical Analyses of Day 9 %ΔALC

Sequence	Point Estimate (%)	90% C.I.
1 (n=11)	-19.7	(-25.0, -12.4)
2 (n=11)	-22.2	(-28.5, -15.9)
3 (n=11)	-30.6	(-36.9, -24.3)

CV181022

Comments:

- A twice daily dosing regimen (q12 h) of 200 mg ketoconazole was selected to ensure adequate tissue and plasma concentrations of the inhibitor over 24 hours. **Considering saxagliptin's half-life (2-3 h), this dosing regimen is acceptable.**
- Ketoconazole was administered for 6 days prior to assessing interaction with saxagliptin. Trough plasma levels of ketoconazole was measured to validate that ketoconazole was at steady-state.
- **Sponsor's cutoff for a significant decrease in ALC was at 30%. The effect was concluded to be less than 30% if the 90% CI for % Δ ALC was entirely above -30%.**
- The clinical significance of the detectable and transient decrease in ALC in Sequence 3 is unknown. However, the magnitude of the decrease upon the re-challenge of the subject with 20 mg saxagliptin co-administered with ketoconazole after a single 20 mg dose of saxagliptin 8 days earlier appeared to be less than that observed in Studies CV181005 and CV181017 where some subjects were considered to be lymphopenic and had flu-like syndrome.

Protocol No.: CV181031

Study Date: 26-Jun-2005 – 20-Aug-2005

Title: Effects on lymphocyte count and the potential for cyanide formation following single and multiple doses of saxagliptin in healthy subjects

This study simultaneously further investigated both the lymphocyte changes upon multiple daily dosing with saxagliptin and also the role of the interrupted dosing in the lymphocyte changes in the same individuals. Due to the presence of a cyano group in the structure of saxagliptin and its active metabolite, BMS-510849, and the preclinical findings in rats, there is a possibility of human exposure to free cyanide (CN⁻) via its metabolic cleavage from saxagliptin. Therefore, information about CN-exposure at the highest Phase 3 dose (10 mg) and a supratherapeutic dose (40 mg) was also determined by the sponsor in this study. Plasma samples for whole blood cyanide and plasma thiocyanate (SCN) concentrations were collected throughout the study. Urine was collected for the measurement of total SCN excretion.

This was a double-blind, multiple-dose, randomized, parallel group, placebo-controlled study in 48 healthy subjects. Flu syndrome had occurred in previous saxagliptin studies, possibly related to dose or intermittent dosing. No flu-like syndrome was observed in the present study. The only treatment Sequence in which absolute lymphocyte count decreases were observed was on Day 23 in subjects administered placebo on Day 1, 40 mg 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). The decreases in absolute lymphocyte count in subjects in Sequence 2 were transient and were most pronounced 24 h following the 40 mg saxagliptin dose on Day 23 (mean decrease of $22 \pm 20\%$ at 24 h post-dose on Day 23).

Maximum percent changes in absolute lymphocyte counts (% Δ ALC) were determined following single and multiple doses of saxagliptin, where

$$\text{Day X \%}\Delta\text{ALC} = \left(\frac{\text{lowest recorded ALC on Day X}}{\text{ALC at corresponding time on Day 1}} - 1 \right) \times 100\%$$

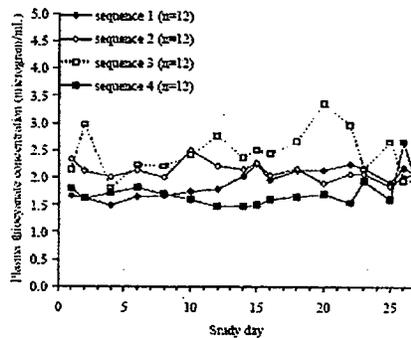
and X=2, or 10, or 15, or 23

$$\text{Day Y \%}\Delta\text{ALC} = \left(\frac{\text{lowest recorded ALC on Day Y}}{\text{ALC at 0 hour on Day 1}} - 1 \right) \times 100\%$$

and Y=4, or 5, or 9, or 11, or 12, or 13, or 17, or 18, or 19, or 25, or 26, or 27.

Dosing with saxagliptin did not appear to have a dose-dependent, time-dependent or sequence-dependent effect on plasma or urine concentrations of thiocyanate.

Mean Plasma Thiocyanate Concentrations Versus Time Profiles Following Interrupted Administration of 10 and 40 mg Saxagliptin



Sequence 1=Single dose 40 mg saxagliptin on Day 2, Placebo on Days 3-9, 40 mg saxagliptin on Days 9-23
 Sequence 2=40 mg saxagliptin on Days 2-15, Placebo on Days 16-22, Single dose 40 mg saxagliptin on Day 23
 Sequence 3=10 mg saxagliptin on Days 2-15, Placebo on Days 16-22, Single dose 10 mg saxagliptin on Day 23
 Sequence 4=Placebo on Days 2-23

Mean (S.D.) Statistics for Amounts of Thiocyanate Recovered in Urine (ug)

Treatment Group	Study Day				
	Day 1	Day 2	Day 10	Day 15	Day 23
Sequence 1 (n=12)	534 (3079)	308 (710)	261 ^a (598)	345 ^a (555)	442 ^b (840)
Sequence 2 (n=12)	1741 (3638)	1477 (2731)	1213 (2380)	634 (1584)	704 (1261)
Sequence 3 (n=12)	794 (1823)	455 (1121)	283 (588)	246 (854)	219 (511)
Sequence 4 (n=12)	830 (1496)	418 (817)	235 (366)	123 (326)	138 (276)

In vitro Studies

Study 930025627: Protein binding

Serum protein binding was determined by equilibrium dialysis method. The concentration of parent and metabolite in the serum protein binding assay was 100 ng/mL. Following completion of dialysis, concentrations of BMS-477118 and BMS-510849 were obtained by analyzing samples from the serum and buffer compartments of the dialysis cell. From each dialysis cell, the free fraction of BMS-477118 and BMS-510849 were calculated as follows:

$$\% \text{ free} = 100 \times (C_{\text{buffer}})/(C_{\text{serum}})$$

Where C_{buffer} is the concentration of BMS-477118 or BMS-510849 in the buffer compartment, and C_{serum} is concentration of BMS-477118 or BMS-510849 in the serum compartment of the dialysis cell. The serum protein binding for saxagliptin and metabolite BMS-510849 was very low in all species tested (Table 1).

Table 1: Free Fraction (%) of BMS-477118 and BMS-510849 in Mouse, Rat, Dog, Monkey and Human Serum (Mean \pm SD, n=3)

	Mouse	Rat	Dog	Monkey	Human
BMS-477118	73.3 \pm 21.5	82.0 \pm 1.5	109.0 \pm 30.2	79.6 \pm 25.5	107.9 \pm 34.2
BMS-510849	109.7 \pm 16.6	104.0 \pm 2.4	97.8 \pm 10.5	89.4 \pm 3.0	103.1 \pm 24

Permeability Studies:

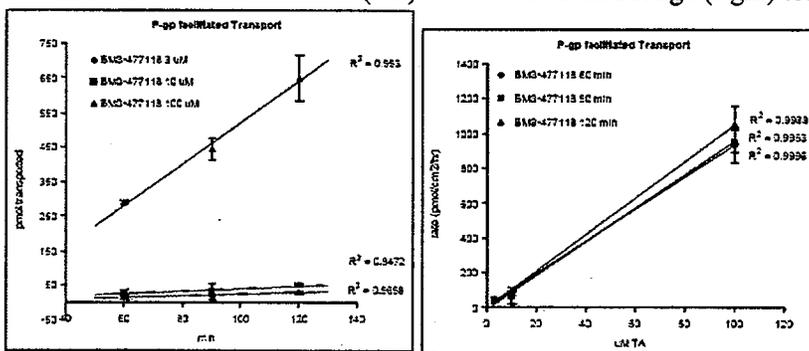
Study 930023241 Title: Evaluation of BMS-477118 Membrane Permeability via dual pH PAMPA (Parallel Artificial Membrane Permeability Assay)

The *in vitro* permeability of BMS-477118 was evaluated using the dual pH Parallel Artificial Membrane Permeability Assay (PAMPA). Dual pH PAMPA consists of a specially formulated lecithin-based lipid combination referred to here as the gastrointestinal tract (GIT) lipid. The GIT lipid is used to form a membrane in a sandwich plate assembly. The permeability coefficient (P_c) values generated in the dual pH PAMPA assay are reported in nm/sec and reflect the ability of a compound to passively cross a lipid membrane. The P_c values (mean \pm SD) of BMS-477118 were 4 ± 1 nm/sec and 59 ± 10 nm/sec at pH 5.5 and 7.4, respectively. These results demonstrate pH dependent intrinsic membrane permeability. BMS-477118 was found to be significantly more permeable at the higher pH tested. Compounds are classified as highly permeable when P_c values are greater than 100 nm/sec and are predicted to be highly absorbed (>75%) in humans if the compound is primarily absorbed via a transcellular route and is not a substrate for active transport mechanisms. These results suggest that BMS-477118 is likely to be minimally absorbed in humans via a transcellular absorption route. It is

important to consider Caco-2 data and other models that include active transport mechanisms when refining *in vivo* activity predictions.

Study report 300861090: Assessment of pgp mediated transport in LLC-PK1 cell monolayers

Time- and concentration dependence of saxagliptin transport was evaluated. The test article was assayed in the A to B and B to A directions in both the P-gp transfected (22L1) and the vector carrying (CLD) cell line at three concentrations (3, 10, 100 μ M). The positive controls used were mannitol, propranolol and digoxin for low, high permeability marker and P-glycoprotein substrate respectively. BMS-477118 transport was linear over the time course (left) and concentration range (right) tested.



Pre-experimental trans-epithelial electrical resistance (TEER), post-experimental lucifer yellow A to B flux values, as well as the digoxin polarization ratio (9.4 fold) were consistent with a properly functioning LLC-PK1 monolayer model. BMS-477118 was subject to active B-A transport with polarization ratios in 22L1 (P-gp expressing) cells approximately 3-fold higher than in CLD (control) cells.

Study report 300877516: Assessment of pgp mediated transport in LLC-PK1 cell monolayers

Porcine kidney-derived, BD C LLC-PK1 cells expressing human P-gp cDNA (designated as 22L1) and the control cell line (LLC-PK1 cells containing the vector without human P-gp cDNA, designated as CLD) were used. Monolayer integrity was evaluated by pre-experimental transepithelial electrical resistance (TEER) measurements and post-experimental lucifer yellow A-to-B flux determinations for each cell monolayer. Time- and concentration dependence of test article transport was evaluated. Saxagliptin was assayed in the A-to-B and B-to-A directions in both the P-gp transfected (22L1) and the vector carrying (CLD) cell line at three concentrations (3, 10, 100 μ M). Samples from the receiver chambers were taken at three time points (60, 90, 120 min) and replaced by an equal volume of receiver solution. The positive controls used were mannitol, propranolol and digoxin for low, high permeability marker and P-glycoprotein substrate respectively. The digoxin polarization ratio in 22L1 was 9.6.

b(4)

BMS-510849 was not subject to active B-to-A transport with polarization ratios in both the 22L1 (P-gp expressing) and CLD (control) cells ranging from 0.8 to 1.1 at the concentrations (3, 10, 100 μM) and time points (60, 90, 120 min) tested.

Map005-477118 Study Title: Preclinical evaluation of the pharmacokinetics and metabolism of BMS-477118

Caco-2 permeability: Caco-2 permeability was determined and the permeability coefficient (Pc) values are expressed as nm/sec. The permeability coefficient (Pc) of BMS-477118 (200 μM) was determined at pH 6.5 along with compounds for which the extent of absorption in humans is known (sulfasalazine, Pc = 19 nm/s, 12% absorbed; metoprolol, Pc = 122 nm/s, 100% absorbed; cimetidine, Pc = 40 nm/s, 70% absorbed, nadolol, Pc = 16 nm/s, 35% absorbed). The permeability of BMS-477118 was found to be 18 nm/sec which was comparable to compounds that exhibit poor absorption (12%) in humans.

P-glycoprotein photoaffinity study: A photoaffinity assay was used to examine if BMS-477118 binds to P-glycoprotein. BMS-477118 (at three different concentrations in the range of 0.5 - 50 μM) was co-incubated with ^{125}I -prazosin (P-glycoprotein probe) along with 10 μg of P-glycoprotein containing membrane in a 96-well plate for 30 min at room temperature. A reduction of ^{125}I -prazosin binding to P-glycoprotein in the presence of a test compound suggests that the test compound may be a P-glycoprotein modulator. For BMS-477118 the percent decrease in radioactive band intensity, which is indicative of prazosin binding, was found to be -21, -5 and 19% at 0.5, 5.0 and 50 μM , respectively.

Protein binding: The extent of protein binding of BMS-477118 was determined in fresh rat, dog, monkey and human sera using ultrafiltration at a concentration of 4332 ng/mL. The binding of BMS-477118 was found to be 20%, 30%, <0.5% and 12% in rat, dog, monkey and human serum, respectively.

Microsomal incubations: The *in vitro* oxidative rates of BMS-477118 were investigated in various animal liver microsomes with the addition of cofactor (NADPH). BMS-477118 was incubated with rat (Sprague-Dawley), dog (beagle), monkey (cynomolgus) or human liver microsomes. The human microsomes were purchased from C and were pooled from 10 individual donors. At 10 μM (4332 ng/mL), the metabolic rates of BMS-477118 in the liver microsomes of rats, dogs, monkeys and humans averaged 0.23, 0.03, 0.14 and 0.06 nmol/min/mg protein, respectively. The rank order of metabolic stability across species is: rat > monkey > human > dog. BMS-477118 does not appear to be a substrate for UGT.

Hepatocyte incubations: The *in vitro* biotransformation rates of BMS-477118 were investigated in various animal hepatocyte suspensions. Preliminary metabolic

b(4)

identification and elucidation was also performed with these incubations. Cryopreserved human hepatocytes were obtained from _____, and were pooled from four donor livers. The rate of metabolism was calculated from the incubation with 5 μ M based on the disappearance of BMS-477118 at the end of the incubation compared to the 0 hr sample. The metabolic rate of BMS-477118 at an initial concentration of 5 μ M was 38, 24, 22 and 8.0 pmol/min/10⁶ cells in rat, dog, monkey and human hepatocytes, respectively.

b(4)

CYP Inhibition: The ability of BMS-477118 to inhibit the major human cytochrome P450 enzymes responsible for the metabolism of drugs was evaluated *in vitro* using recombinant human CYP enzymes. IC₅₀ values for inhibition of the de-ethylation of 3-cyano-7-ethoxycoumarin (CEC; CYP1A2 and CYP2C19), the inhibition of the dealkylation of dibenzylfluorescein (DBF; CYP2C9), and the de-ethylation of 3-[2-(N,N-diethyl-Nmethylamino) ethyl]-7-methoxy-4-methylcoumarin (AMMC; CYP2D6) by BMS-477118 were determined. The ability of BMS-477118 to inhibit CYP3A4 was evaluated by monitoring the dealkylation of 7-benzyloxy-4-(trifluoromethyl)-coumarin (BFC) and the dealkylation of resorufin benzyl ether (BzRes). BMS-477118 was a very weak inhibitor of human CYP1A2, CYP2C9, CYP2C19, CYP2D6 and 3A4 (IC₅₀ > 100 μ M for all isoforms tested).

CYP substrate specificity: The investigation of specific CYP enzymes which mediate the metabolism of BMS-477118 was performed. BMS-477118 was incubated with human liver microsomes along with compounds specific for the inhibition of individual CYP enzymes commonly involved in drug metabolism. The human microsomes were purchased from _____ and were pooled from 10 individual donors. The metabolism of BMS-477118 in human liver microsomes was significantly inhibited by ketoconazole (60%) and troleandomycin (85%), both CYP3A4-specific inhibitors, suggesting that CYP3A4 is partly responsible for the metabolism of the compound. Inhibition of BMS-477118 was noted in the presence of tranlylcypromine (2C19, 35%) and quinidine (2D6, 35%). The rates of metabolism by expressed human enzymes indicate that BMS-477118 is metabolized by CYP1A2 and CYP3A4. These results, along with the CYP-specific inhibitor data, indicate that BMS-477118 is likely to be a substrate for human CYP3A4 *in vivo* and may be a substrate for CYP1A2, 2C19 and 2D6.

b(4)

Study 930024169 Title: Transporter phenotyping studies with saxagliptin (BMS-477118) and BMS-510849 (5-hydroxy metabolite of saxagliptin)

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 validity of the transfected cell models was established by performing uptake studies with positive controls. The uptake of the following positive control compounds was evaluated in parallel with saxagliptin and BMS-510849; [³H]estradiol-17β-D-glucuronide (E-glu) for OATP1B1, [³H]BQ-123 for OATP1B3, [³H]1-methyl-4 phenylpyridinium(MPP) for OCT1 and OCT2, [³H]*para*-aminohippurate (PAH) for OAT1, [³H]estrone-3-sulfate (E3S) for OAT3, and [¹⁴C]glycylsarcosine (Gly-Sar) for PEPT1. As an inhibitor of each transporter, the following compounds were used: bromosulphophthalein (BSP, 50 μM) for OATP1B1 and 1B3, imipramine (200 μM) for OCT1 and OCT2, probenecid (0.5 mM) for OAT1, bumetanide (200 μM) for OAT3, and Gly-Sar (10 mM) for PEPT1. *Xenopus laevis* oocytes injected with cRNA of human OAT3, OCT1, and PEPT2 were purchased from C) and uptake studies were conducted 4 days post-injection.

b(4)

The results show that both saxagliptin and its active metabolite (BMS-510849) are not substrates of these transporters *in vitro*.

930018000 Study: Evaluation of Transcellular Permeability of BMS-477118 Through Caco-2 Cells

The objective of this study was to evaluate the *in vitro* permeability of BMS-477118 using Caco-2 cells. The apical-to-basolateral permeability (absorptive direction) of BMS-477118 was measured at 3 different apical pHs (5.5, 6.5 and 7.4, n=3 for each pH). The initial concentration of BMS-477118 used was 200 μM. The apical to basolateral Pc (mean±SD, n=3) of BMS-477118 was 10±2, 17±11 and 12±1 at an apical pH of 5.5, 6.5 and 7.4, respectively. These results suggested that BMS-477118 would be poorly absorbed in humans *via* transcellular route despite adequate absorption observed in pre-clinical animal models BMS-477118 has a good potential to be absorbed *via* paracellular pathway *in vivo*. The integrity of monolayer has been confirmed by a validated procedure using mannitol as the hydrophilic marker. *Comment:* The Pc of mannitol was <20 nm/sec. Only high concentration of saxagliptin was used in this study.

CYP Inhibition/Induction studies:

Study pd278604: In Vitro Evaluation of BMS-510849 as an Inhibitor of Human CYP Enzymes

The potential of BMS-510849 to inhibit nine specific CYP enzymes was evaluated in pooled human liver microsomes. The IC₅₀ values were determined using probe substrates for CYP1A2 (phenacetin), CYP2A6 (coumarin), CYP2B6 (bupropion), CYP2C8 (paclitaxel), CYP2C9 (tolbutamide), CYP2C19 ((*S*)-mephenytoin), CYP2D6 (bufuralol), CYP2E1 (chlorzoxazone), and two substrates for CYP3A4 (midazolam and testosterone) at single concentrations approximating their apparent K_m values. The concentrations of BMS-510849 used for these IC₅₀ studies were 0,

0.1, 1, 10, 50, and 200 μ M. Time-dependent inhibition screening was done by pre-incubation for 15 minutes at 37 °C with 0, 0.1, 1, 10, 50, and 200 μ M BMS-510849 in the presence of 1 mM NADPH. The list of inhibitors used is shown in the following table.

CYP Enzyme	Direct Inhibitor	Mechanism-Based Inhibitor
CYP1A2	α -Naphthoflavone	Furafylline
CYP2A6	Pilocarpine	8-Methoxypsoralen
CYP2B6	Oxphandrine	ThioTEPA
CYP2C8	Quercetin	1-Aminobenzotriazole
CYP2C9	Sulfaphenazole	Suprofen
CYP2C19	Modafinil	Ticlopidine
CYP2D6	Quinidine	3,4-Methylenedioxyamphetaminine
CYP2E1	4-Methylpyrazole	Phenethyl isothiocyanate
CYP3A4	Ketoconazole	Mifepristone

Appropriate positive controls were used in this study. Incubation of BMS-510849 in microsomal suspensions at concentrations in the range of 0.1 to 200 μ M resulted in no concentration dependent inhibition >50% for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

The percent remaining activity of microsomes pre-incubated for 15 minutes with BMS-510849 and NADPH were compared to microsomes pre-incubated with NADPH and no BMS-510849. No inhibition >50% was observed with pre-incubated samples for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Overall conclusions: Incubation of BMS-510849 in human hepatic microsomal suspensions at concentrations \leq 200 μ M 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.

Study pd227204: In Vitro Evaluation of BMS-477118 as an Inhibitor of Human CYP Enzymes

The potential of saxagliptin to inhibit nine specific CYP enzymes was evaluated in pooled human liver microsomes. The IC₅₀ values were determined using probe substrates for CYP1A2 (phenacetin), CYP2A6 (coumarin), CYP2B6 (bupropion), CYP2C8 (paclitaxel), CYP2C9 (tolbutamide), CYP2C19 ((*S*)-mephenytoin), CYP2D6 (bufuralol), CYP2E1 (chlorzoxazone), and two substrates for CYP3A4 (midazolam and testosterone) at single concentrations approximating their apparent K_m values. The use of positive control inhibitors demonstrated that the respective CYP enzymes could be inhibited under the experimental conditions. All direct inhibitors inhibited the reactions by greater than 50% when compared to the control incubations and all mechanism-based positive control inhibitors (see table above) demonstrated greater inhibition with a 15 minute pre-incubation.

Incubation of BMS-477118 in microsomal suspensions at concentrations in the range of 0.1 to 50 μ M resulted in no concentration dependent inhibition >50% for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The percent remaining activity of microsomes pre-incubated for 15 minutes with BMS-

477118 and NADPH were compared to microsomes pre-incubated with NADPH and no BMS-477118. No inhibition >50% was observed with pre-incubated samples for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Study 930015211: *In Vitro* Assessment of BMS-477118 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

The aim of this study was to utilize primary cultures of human hepatocytes to model the potential of BMS-477118 to induce the cytochrome P450 enzymes 1A2, 2B6, 2C9 and 3A4. Enzymatic activity and levels of mRNA encoding these enzymes were determined after treatment with BMS-477118 at concentrations of 0.2, 1.0, 5.0, and 25 μ M once daily for three consecutive days in three separate preparations of human hepatocytes (Hu211, Hu224, and Hu223). Results were compared to those obtained from hepatocyte cultures treated with known cytochrome P450 inducers 3-methylcholanthrene (3-MC, CYP1A2 inducer), phenobarbital (CYP2B6 inducer) and rifampicin (CYP2C9 and CYP3A4 inducer).

Treatment of primary cultures of human hepatocytes for 3 consecutive days with BMS- 477118 at 4 concentrations (0.2, 1.0, 5.0 and 25 μ M) revealed no marked dose-dependent increases in enzyme activity of CYP1A2 (phenacetin *O*-deethylation), CYP2B6 (bupropion hydroxylation), CYP2C9 (diclofenac 4'-hydroxylation) or CYP3A4 (testosterone 6 β - hydroxylation), compared to that of vehicle control. Enzyme activities were enhanced over negative controls in the three cultures treated with prototypical inducers: CYP1A2 activity (15-20 fold with 3-MC), CYP2B6 activity (8-13 fold with phenobarbital), CYP2C9 activity (~2-fold with rifampicin), and CYP3A4 activity (3-6-fold with rifampicin; 3-5 fold with phenobarbital) indicating that the cells were responding appropriately to the prototypical inducers. RT-PCR (TaqMan) analysis revealed no marked increases in levels of CYP1A2, CYP2B6 and CYP3A4 mRNA relative to negative controls in hepatocytes treated with BMS-477118, while there were large increases (6-385-fold) in hepatocytes cultures treated with the corresponding prototypical inducers. A moderate increase in CYP2C9 mRNA levels (1-4-fold) was observed for the three donors after treatment of BMS-477118. (The CYP2C9 activity was increased in one, Hu221 sample about 1.6-1.8 fold over control; 53-65% of control). In comparison, mRNA levels increased 3-5-fold in the three cultures treated with rifampicin.

Comment: At the concentrations tested (0.2-25 μ M), exposure of human hepatocytes to BMS-477118 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 hepatocytes.

Study pd278704: *In Vitro* Assessment of BMS-510849 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

The potential of BMS-510849 to induce the cytochrome P450 enzymes 1A2, 2B6, 2C9 and 3A4 was determined in primary cultures of human hepatocytes. Effect on enzymatic activity and levels of mRNA encoding these enzymes were determined after treatment with BMS-510849 at concentrations of 0.2, 1.0, 10, and 100 μ M once daily for three consecutive days in

three separate preparations of human hepatocytes. Results were compared to those obtained from hepatocyte cultures treated with known cytochrome P450 inducers 3-methylcholanthrene (3-MC, CYP1A2 inducer), phenobarbital (CYP2B6 inducer) and rifampicin (CYP2C9 and CYP3A4 inducer).

Enzyme activities were enhanced relative to vehicle control (0.1%DMSO) in the three cultures treated with prototypical inducers: CYP1A2 activity (16-20 fold with 3-MC, 2 μ M), CYP2B6 activity (8-13 fold with Phenobarbital, 1000 μ M), CYP2C9 activity (1.9-2.2 with rifampicin, 10 μ M) and CYP3A4 activity (3.3-6.0 fold with rifampicin, 10 μ M), indicating that the cells were responding appropriately to prototypical inducers.

After three days, there was no marked dose-dependent increases in the enzyme activity of CYP1A2 (phenacetin *O*-deethylation), CYP2B6 (bupropion hydroxylation), CYP2C9 (diclofenac 4' -hydroxylation) or CYP3A4 activity (testosterone 6 β -hydroxylation) compared to that of vehicle controls. One hepatocyte preparation (donor 1, Hu211) revealed a moderate increase as compared to positive control in CYP2C9 activity (1.2 - 1.6-fold) and an increase in CYP3A4 activity (2-fold) at 10 and 100 μ M BMS-510849. CYP2C9 activity was not elevated with the hepatocyte preparations Hu223 and Hu224 that were treated with BMS-510849

Hepatocytes treated with the prototypical inducers exhibited enhanced mRNA levels relative to negative controls: 71-385 fold increase in CYP1A2 mRNA with 3-MC, 6-29 fold increase in CYP2B6 mRNA with phenobarbital and 7-11 fold increase in CYP3A4 mRNA with rifampicin. RT-PCR (TaqMan) analysis revealed no marked increases in levels of CYP1A2, CYP2B6 or CYP3A4 mRNA in hepatocytes treated with BMS-510849. CYP2C9 mRNA levels were increased in all the three hepatocytes (1.5-2.7 fold) with BMS-510849, relative to a 3-5-fold increase with rifampicin and a 3-6 fold increase over control with phenobarbital.

Comment: At the concentrations tested (0.2-100 μ M), exposure of human hepatocytes to BMS-477118 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.

Hu211 hepatocyte showed induction of CYP2C9 mRNA in response to both saxagliptin and BMS-510849.

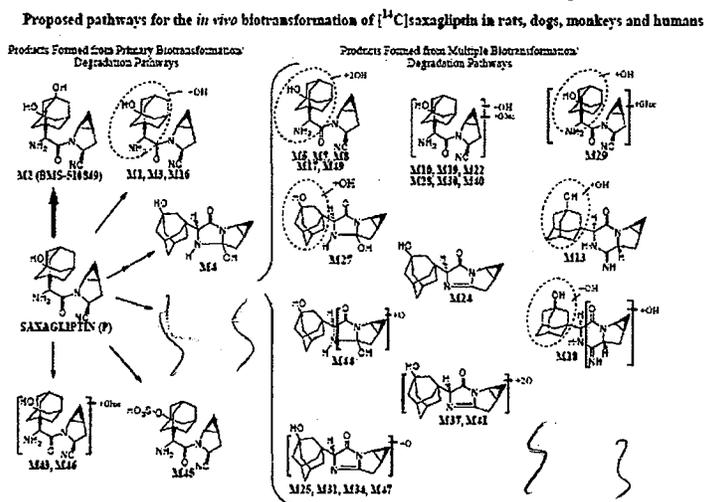
Study 930016961 Title: Comparative Biotransformation of [14C]Saxagliptin after Oral Administration to Bile-Duct Cannulated Rats, Intact Rats, Dogs, Monkeys, and Humans

The proposed pathways for the *in vivo* biotransformation of [14C]saxagliptin in rat, dog, monkey and human are illustrated in Figure 2. 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 included the following:

- Hydroxylation at other positions on the amino-methyl-adamantyl group.
- Direct sulfate conjugation of the parent compound.
- Glucuronide conjugation of the parent compound or the monohydroxylated metabolites.
- Oxidation to form a cyanohydrin intermediate, followed by de-cyanation and cyclization to form metabolites having a keto-imidazolidine structure; dehydration to form an imidazoline.
- Products resulting from a combination of the above pathways.

Urinary excretion was a major route in all species (97% in humans). Fecal excretion was 22.1%. All metabolites that were detected in humans were also detected in at least one other species. Unchanged drug and BMS-510849 were the major components in the plasma. In humans, no component other than saxagliptin or BMS-510849 accounted for more than 3.8% of the excreted dose or more than 3.7% of the plasma radioactivity.



Study 930024372 title: Investigation of the Enzymes Involved in the *In Vitro* Formation of BMS-510849 from Saxagliptin in Humans, and Kinetics of BMS-510849 Formation

When saxagliptin was incubated with HLM in the presence of ketoconazole (1 μ M), a direct inhibitor of CYP3A4/5, or toleandomycin (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.

The CYP3A4/5 antibody was the only monoclonal antibody that significantly inhibited the metabolism of saxagliptin to BMS-510849. When saxagliptin was incubated in HLM

in the presence of anti-CYP3A4, the formation of BMS-510849 was inhibited by >89%. In the presence of antibodies against other CYP enzymes (anti- 1A2, 2B6, 2C8, 2C19 and 2D6), the formation of BMS-510849 was not affected.

Saxagliptin, at a concentration of 5 μM , was incubated with HLM (0.1, 0.25, or 0.5 mg/mL) or cDNA-expressed CYP3A4 (10, 25, 50 or 100 pmol/mL), for 0, 5, 10, 15, 30 and 60 min to establish the appropriate incubation conditions for additional experiments. Incubations with HLM (0.25 mg/mL) for 30 min and CYP3A4 (10 pmol/mL) for 10 min resulted in a linear rate of BMS-510849 formation and <15% depletion of saxagliptin over the incubation interval. Data from incubations with HLM, CYP3A4 and CYP3A5 at 12 concentrations of saxagliptin (1, 5, 10, 30, 50, 100, 200, 300, 400, 500, 600 and 800 μM) were used to determine K_m and V_{max} values for BMS-510849 formation. The formation of BMS-510849 from saxagliptin in HLM, expressed CYP3A4 and expressed CYP3A5 followed Michaelis-Menten Kinetics. The K_m values for the formation of BMS-510849 were 94.8 μM , in HLM, 81.7 μM in CYP3A4, and 252 μM in CYP3A5.

The plasma C_{max} of saxagliptin after oral administration of a 10 mg dose of saxagliptin, the highest dose employed in Phase 3 clinical studies, was 0.14 μM (45 ng/mL).⁵ Although the concentrations of saxagliptin (1 and 10 μM) selected for use in the correlation and CYP inhibition experiments were higher than the plasma C_{max} , they were considered to be appropriate for use in these experiments since they were below the K_m values in HLM.

Study ddb018-477118: *In Vitro* Biotransformation of [¹⁴C]BMS-477118 in Mouse, Rat, Dog, and Human Liver Microsomes, and in cDNA-Expressed Human CYPs.

Biotransformation profiles of BMS-477118 were determined in liver microsomes from CD-1 mouse, Sprague-Dawley rat, beagle dog, and human (pooled from 20 donors), and also in microsomes containing cDNA-expressed human CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, or 3A5 isozymes. Incubations were carried out with [¹⁴C]BMS-477118 at initial concentrations of 10 μM at 37°C for 1 h with liver microsomes, and for 30 min with cDNA-expressed human CYP isozymes. BMS-477118 was biotransformed to three hydroxylated metabolites (M1, M2, and M3). The major metabolite was M2 and accounted for 42%, 41%, 13%, and 23% of the total radioactivity, respectively, in mouse, rat, dog, and human liver microsomes. Overall, the extent of microsomal metabolism of BMS-477118 was rat-human>mouse>>dog. BMS-477118 was metabolized by cDNA-expressed CYP3A4 and 3A5, but not by 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, and 2E1. All three metabolites M1, M2, and M3, and the degradant D1 were also observed in cDNA-expressed human CYP3A4 and 3A5 microsomal incubations with BMS-477118. No metabolism of BMS-477118 was observed with CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, and 2E1 isozymes and BMS-477118.

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. All of the human metabolites of BMS-477118 were observed in incubations with microsomes from the other three species. The major metabolite of BMS-477118 was M2 in all species and was identified as BMS-510849, a mono-hydroxylated derivative of BMS-477118. CYP3A4 and CYP3A5 were the only human CYP isoforms involved in the metabolism of BMS-477118.

Study 930021240 title: Measurement of Cyanide Release from Saxagliptin (BMS-477118) and BMS-510849 in Liver Microsomal and Expressed-Enzyme Systems.

The objectives of this study were: 1) to quantify cyanide formation after *in vitro* incubation of saxagliptin and BMS-510849 with mouse (male), rat (male and female), dog (male), monkey (male and female), and human (male and female pooled) liver microsomes and expressed CYPs enzymes from rats (CYP2C11, 2C12, 2C13) (CYP2C21) and human (CYP2C8, 2C18, 2C19) and 2) to determine the effect of cimetidine, a CYP2C11 inhibitor, on the formation of cyanide in selected *in vitro* systems.

Humans: Smaller amounts of cyanide formation were measured in the incubations of saxagliptin (100 μM) with CYPs 2C8 (final cyanide concentration = 1.7 μM) and 2C19 (final cyanide concentration = 1.4 μM). The amount of cyanide measured was below the lower limit of quantitation (LLOQ = 0.77 μM) for CYP2C9 and 2C18 incubations. Cyanide formation in the incubations of BMS-510849 with expressed CYPs were all below the lower limit of quantitation (<0.77 μM).

Cyanide was detected at a final concentration of 42 μM in the incubation of saxagliptin (100 μM) with expressed CYP2C11. Cyanide formation was the most abundant in the incubations of saxagliptin with expressed CYP2C11, a male-selective rat liver enzyme.

Chiral conversion:

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 formation of any of these diastereomers is not anticipated to occur with saxagliptin through any typical mechanism of metabolic chiral inversion (i.e., oxidation of a secondary alcohol, conjugation of a carboxylic acid with acetyl CoA) because metabolism of saxagliptin through these pathways was not observed in the human ADME study (CV181004) which showed either direct excretion of parent or hydroxylation of the adamantane moiety as the major clearance routes. However, there is a potential for chiral inversion through chemical mechanisms, either *in vivo* or *ex vivo* during sample storage or processing. For these

reasons the presence of two of the diastereomers (BMS-573659 and BMS-644448, Figure 1) in human samples was investigated.

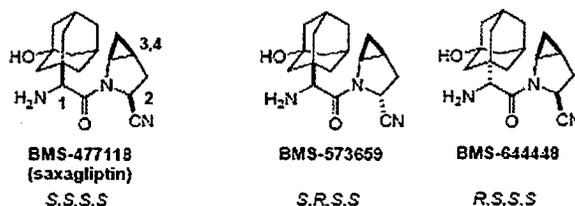


Figure 1: Structures of saxagliptin and diastereomers

The chromatograms from 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 is concluded that these components were not present in these human samples. To further investigate the potential for formation of diastereomers of saxagliptin under biological conditions BMS-573659 and BMS-644448 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.

Single Ascending Dose Study CV181001

Title:

“Placebo-controlled, ascending single-dose study to evaluate the safety, pharmacokinetics, and pharmacodynamics of BMS-477118 in healthy subjects”

Objectives:

The primary objective of this study was to assess the safety and tolerability of a single dose of BMS-477118 in the range of 1.0 to 100 mg. As secondary objective, the pharmacokinetics of the drug BMS-477118 and the major metabolite BMS-510849 under fasted and fed conditions as well as the pharmacodynamic effects were evaluated.

Study design:

This was a placebo-controlled, two period, sequential, ascending single-dose designed study, which enrolled seventy-two (72) healthy subjects assigned to 9 sequential panels (1, 2.5, 5, 10, 20, 30, 50, 75 and 100 mg or matched placebo).

Pharmacokinetic sample collection was performed prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 10, 12, 24, 36, and 48 hours post dosing.

Results:

Adverse events:

Thirty-four adverse events were reported in 21 (29%) of the subjects. 22 AE's considered by the investigator to be possibly related to the study drug and 2 subjects discontinued participation in the study.

Pharmacokinetics:

All concentration for BMS-477118 and BMS-510849 ate the 1 mg dose were below the LLOQ. Pharmacokinetic parameters obtained from study CV181001 for doses ranging from 1 to 100 mg are presented in the table below:

Table 1 Pharmacokinetic parameter ranges for BMS-477118 and BMS-510849 in human plasma

Pharmacokinetic Parameter	BMS-477118		BMS-510849	
	Fasted (range)	Fed (range)	Fasted (range)	Fed (range)
mean T-half (h)	1.2-2.8	2.3-3.4	2.8-6.7	2.9-4.0
median Tmax (h)	0.50-1.00	0.75-3.00	1.00-2.00	1.50-4.00
mean CLR (mL/min)	150-237	121-252	52-114	54-123

Study CV181001 provides information about the inter subject variability in the pharmacokinetic parameters. The inter subject variability for AUC_(0-inf) and C_{max} for BMS-477118 and BMS-510849 is presented in the table below:

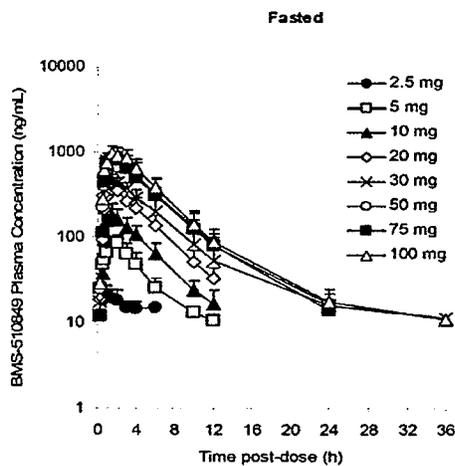
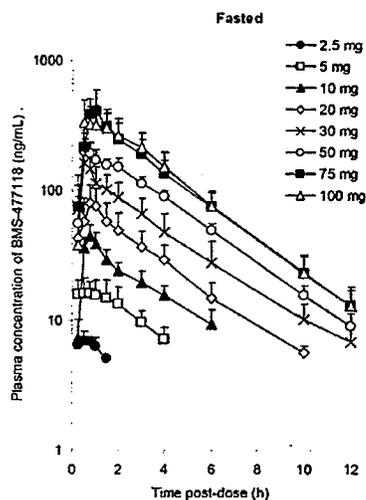
Table 2 Pharmacokinetic parameter variability for BMS-477118 and BMS-510849 in human plasma

Dose (mg)	C _{max}		AUC _(0-inf)	
	BMS-477118	BMS-510849	BMS-477118	BMS-510849
Plasma				
2.5	8.88%	29.17%	27.26%	91.55%
5	14.20%	23.52%	23.31%	24.81%

Figure 1. Mean (plus SD) plasma concentration for BMS-477118 and BMS 510849 following administration of 1 to 100 mg of BMS-477118 to healthy subjects in fasted state.

BMS-477118

BMS-510849



Coadministration of food slightly decreased C_{max} of BMS-477118 with a 28% reduction in geometric means for doses ranging from 2.5 to 50 mg and slightly increased the $AUC_{(inf)}$ of BMS-477118 for doses ranging from 2.5 to 30 mg.

The effect of food was larger at lower doses. At higher doses, food did not appear to have an effect on $AUC_{(inf)}$. Only slight decreases in C_{max} and $AUC_{(inf)}$ were observed for BMS-510849 when BMS-477118 was coadministered with food.

The maximum Percent Cumulative Amount (%) per dose excreted in urine ranges from 5.2% to 26.9% and 19.1% – 67.2% for BMS-477118 and BMS510849 respectively under fasting conditions.

The maximum Percent Cumulative Amount (%) per dose excreted in urine ranges from 4.9% to 34.5% and 5.4% – 75.0% for BMS-477118 and BMS510849 respectively under fed conditions.

Pharmacodynamics: Dosing with BMS-477118 resulted in inhibition of DDP-IV activity. DPP-IV inhibition peaked between 0.75 and 2 hours when the dose was administered under fasting conditions. The mean (S.D.) inhibition at 24 h for the 2.5 and 5 mg dose was 35% (4) and 44% (7) respectively. The maximum inhibition for the 2.5 mg dose was 73% and was reported approximated between 0.5 and 6 h post dosing. The maximum inhibition for the 5 mg dose was 79% and was reported approximated between 1 and 6 h post dosing.

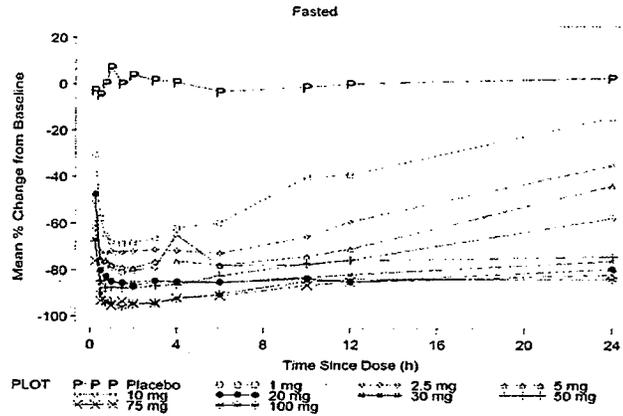


Figure 2 Plot of mean percent changes from baseline for plasma DPP_IV activity over 24 hour since dosing (fasted)

On average plasma active GLP-1 concentrations peaked between 10 and 12 hours for subjects receiving BMS-477118 under fasting conditions, and either after breakfast (between 0.5 and 1 hour after dosing) or after the evening meal (between 10 and 12 hours after dosing) for subjects receiving BMS-477118 under fed conditions.

Analytical method:

The active moieties were measured in human k₃EDTA plasma using liquid chromatography/tandem mass spectrometry, after online extraction and turboionspray ionization.

Following are the assay parameters for the bioanalytical assay:

	<i>Plasma</i>		<i>Urine</i>	
	BMS	()	BMS	()
BMS-477118				
Standard curve range	5-1000 ng/mL		25-5000 ng/mL	
LLOQ	5 ng/mL		25 ng/mL	
CV%	3.6%	4.1%	5.0%	10.3%
Deviation from nominal concentration	±1.7%	±6.0%	±3.0%	±6.6%
BMS-510849				
Standard curve range	10.0-2000 ng/mL		50-10,000 ng/mL	
LLOQ	10 ng/mL		50 ng/mL	
CV%	6.9%	4.7%	9.5%	3%
Deviation from nominal concentration	±3.0%	±4.8%	±3.0%	±8.8%

b(4)

Reviewer's comment:

- A definitive food effect study (CV181034) was conducted by the sponsor.
- The effect of food on the $AUC_{(inf)}$ was larger at lower doses. Since doses of 2.5 and 5 mg are the to-be-marketed doses, the extend of the food effect should be evaluated from the results of the definitive food effect study (CV181034).
- Accuracy and precision of the analytical runs seem acceptable, however an evaluation was performed to assess the influence of other mono-hydroxylated metabolites with the same mass spectral characteristics as BMS-510849 on the pharmacokinetic results. 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.

Mass balance and metabolism study CV181004**Title:**

“Mass balance and metabolism of [14c] bms-477118 in healthy male subjects”

Objectives:

The primary objective of this study was to assess the pharmacokinetics, metabolism, and routes and extent of elimination whereas the secondary objective was to assess the safety of 50 mg (91.5 μ Ci) [14C]-saxagliptin.

Study Design:

This was an open-label, non-randomized, single dose study, which enrolled 6 male subjects. Subjects received a single oral dose of 50 mg [14C]-saxagliptin solution containing 91.5 μ Ci of total radioactivity.

Sample collection:

Blood samples were collected pre-dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168 hours post dosing. Urine and feces were collected over 12 and 24 hours intervals respectively from 0-168 hours. All specimens were analyzed for total radioactivity (TRA).

Results:**Absorption:**

Assuming no physical degradation or metabolism in the intestinal tract or subsequent absorption of radiolabeled degradants at least 74.9% of an oral dose of saxagliptin were absorbed. Saxagliptin and BMS-510849 account for 97.78% of the total radioactivity of the mean $AUC_{(inf)}$. [other minor monohydroxylated metabolites might be included due to incomplete assay specificity]

Distribution In Whole Blood:

The mean ratio of plasma: blood TRA $AUC_{(inf)}$ in this study was 1.20

Metabolism:

Plasma exposure of BMS-510849 plus other minor monohydroxylated metabolites was 3.31 times higher than the parent drug. The similarity in half life of parent drug and metabolite suggest formation limited clearance of BMS-510849. Overall, 15.36% of the dose might be attributed to other minor metabolites however their systemic concentration appears to be low since only <2,5% of the plasma TRA was unaccounted for.

Renal Excretion:

74.9% of the radioactivity of the administered dose was excreted in urine.

Saxagliptin (23.53%) and BMS-510849 plus other minor monohydroxylated metabolites (35.74%) account for 59.27% of the administered dose excreted in urine. 15.6% of the administered dose were other minor metabolites. The mean renal clearance of saxagliptin in this study (234 mL/min) suggests active renal secretion. The mean renal clearance for BMS-510849 plus other minor monohydroxylated metabolites (102 mL/min) is comparable to the glomerular filtration rate.

Fecal Excretion:

A mean of 22.05% of the administered saxagliptin dose was recovered in feces. Fecal recovery could be from unabsorbed drug or biliary excretion. 8.4% and 0.5% of the administered dose are excreted fecally as BMS-510849 and saxagliptin respectively.

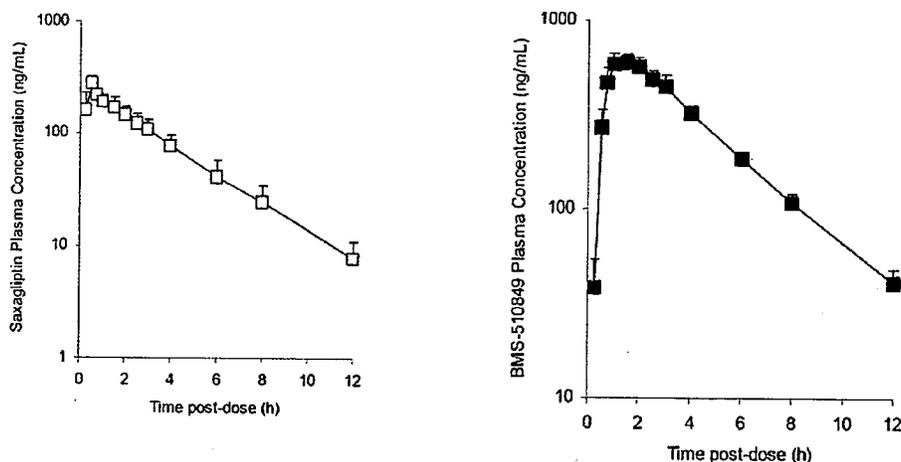


Figure 3. mean plasma concentration-time profile (\pm SD) in healthy male volunteers for saxagliptin (\square) and BMS-510849 (\blacksquare) following administration of a single oral dose of 50 mg 14 C-Saxagliptin.

Analytical method:

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

Following are the assay parameters for the bioanalytical assay:

	<i>Plasma</i>	<i>Urine</i>	
	BMS		(
BMS-477118			
Standard curve range	5-1000 ng/mL	25-5000 ng/mL	
LLOQ	5 ng/mL	25 ng/mL	
CV%	Intrarun CV% 3.0%	Intrarun CV% 3.0%	Interrun CV% 4.7%
Deviation from nominal concentration	±8.6%	±1.8%	
BMS-510849			
Standard curve range	10.0-2000 ng/mL	50-10,000 ng/mL	
LLOQ	10 ng/mL	50 ng/mL	
CV%	Intrarun 8.7%	Intrarun CV% 4.8%	Interrun CV% 0.0%
Deviation from nominal concentration	±5.8%	±2.4%	

b(4)

Reviewer's comment:

- Accuracy and precision of the analytical runs seem acceptable, however an evaluation was performed to assess the influence of other mono-hydroxylated metabolites with the same mass spectral characteristics as BMS-510849 on the pharmacokinetic results. 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.
- Data for subject 6 was excluded from the analysis for urinary recovery and total radioactivity. Urinary recovery for subject 6 was approximately half the recovery of the other subjects. The sponsor states that this was due to incomplete urine collection of this subject during the 0-12h interval.

Relative bioavailability study CV 181037

Title:

“Study Of The Bioavailability And Pharmacodynamics Of Saxagliptin Administered In 1 X 5 Mg Tablet Relative To Saxagliptin Administered In 1 X 5 Mg Capsule In Healthy Subjects”

Objective:

To assess the bioavailability and pharmacodynamics of saxagliptin administered in 1 x 5 mg tablet relative to saxagliptin administered in 1 x 5 mg capsule.

Batches used:

Reference product (Treatment A):

- 1 x 5 mg capsule, Product Identification Number BMS-477118-R005-002, Formulation: BMS-477118-08 Capsule

Test product (Treatment B):

- 1 x 5 mg tablet, Product Identification Number: BMS-477118-K005-111, Formulation: BMS-477118-11 film coated tablet

Results:

Figure 4 Mean (+ SD) plasma concentration-time profiles for saxagliptin (BMS-477118, left) and BMS-510849 (right) following administration of a single oral 1 x 5 mg dose of saxagliptin as a capsule (n=15, treatment A) or 1 x 5 mg dose of saxagliptin as a tablet (n=15, treatment B)

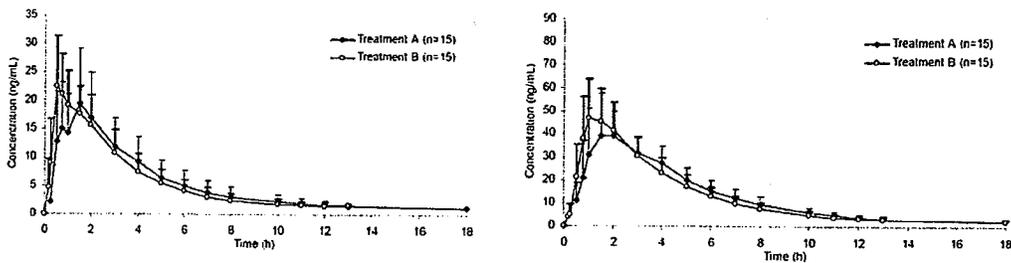


Table 3 Statistical analyses for Saxagliptin pharmacokinetic parameters (treatment A= 1 x 5 mg saxagliptin capsule, treatment B= 1 x 5 mg tablet)

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)	21.99	24.46	1.112 (0.933,1.326)
AUC(INF) (ng•h/mL)	80.81	77.44	0.958 (0.897, 1.024)
AUC(0-T) (ng•h/mL)	75.33	72.75	0.966 (0.900, 1.036)

Table 4 Statistical analyses for BMS-510849 pharmacokinetic parameters (treatment A= 1 x 5 mg saxagliptin capsule, treatment B= 1 x 5 mg tablet)

Pharmacokinetic Parameter	Treatment A (n = 15)	Treatment B (n = 15)
C _{max} (ng/mL) Geometric Mean (CV%)	43.23 (36)	47.24 (32)
T _{max} (h) Median (min, max)	2.00 (1.00, 4.00)	1.50 (0.75, 2.00)
AUC(0-T) (ng•h/mL) Geometric Mean (CV%)	209.12 (21)	202.52 (27)
AUC(INF) (ng•h/mL) Geometric Mean (CV%)	222.14 (21)	214.47 (27)
T-half (h) Mean (SD)	3.51 (0.85)	3.13 (0.85)

Reviewer's comment:

- The tablet formulation meets the bioequivalence criteria for AUC_{inf} and AUC_{0-t} but is outside the 80-125% boundaries for the 90% confidence interval in regards to C_{max}.
- PK parameters of the main metabolite BMS510849 seem similar, however C_{max} for the test product is ~10% higher

Relative bioavailability study CV 181003

Title:

“Bioavailability of BMS-477118 Administered As 1 X 40 Mg Tablet Relative To BMS-477118 Administered As 2 X 20 Mg Capsules In Healthy Subjects”

Objective:

To assess the bioavailability of saxagliptin administered in 1 x 40 mg tablet relative to saxagliptin administered in 2 x 20 mg capsules

Batches used:

Reference product (Treatment A):

- 2 x 20 mg capsule, Product Identification Number BMS-477118-R020-004,
Formulation: BMS-477118-08 Capsule

Test product (Treatment B):

- 1 x 40 mg tablet, Product Identification Number: BMS-477118-K040-107,
Formulation: BMS-477118-11 film coated tablet

Results:

Figure 4 Mean (+ SD) plasma concentration-time profiles for saxagliptin (BMS-477118, left) and BMS-510849 (right) following administration of a single oral 1 x 40 mg dose of saxagliptin as a tablet (n=16, -o-) or 2 x 20 mg dose of saxagliptin as capsules (n=16, -■-)

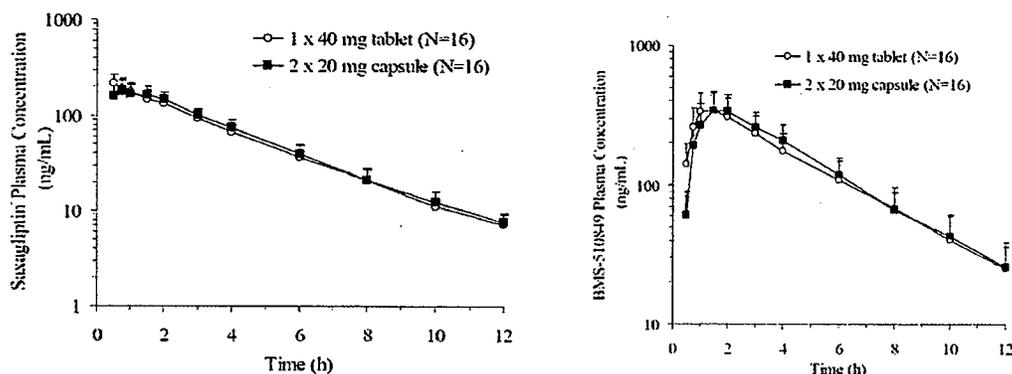


Table 5 Results of Statistical analyses on saxagliptin pharmacokinetic parameters

Pharmacokinetic Parameter	Geometric Means		Tablet/Capsules Ratio of Geometric Means	
	Saxagliptin 2 x 20mg Capsules	Saxagliptin 1 x 40mg Tablet	Point Estimate	90% C.I.
Cmax (ng/mL)	199	220	1.11	(1.03, 1.19)
AUC(INF) (ng/mL·h)	721	706	0.98	(0.94, 1.02)
AUC(0-T) (ng/mL·h)	696	682	0.98	(0.94, 1.02)

Table 6 Results of Statistical analyses on BMS-510849 pharmacokinetic parameters

Pharmacokinetic Parameter	Treatment	
	Saxagliptin 2 x 20mg Capsules (n=16)	Saxagliptin 1 x 40mg Tablet (n=16)
Cmax (ng/mL) Geometric Mean (C.V. %)	340 (31)	330 (35)
AUC(INF) (ng/mL·h) Geometric Mean (C.V. %)	1659 (28)	1593 (34)
AUC(0-T) (ng/mL·h) Geometric Mean (C.V. %)	1590 (29)	1521 (35)
Tmax (h) Median (Min, Max)	1.50 (1.00, 3.00)	1.50 (1.00, 3.00)
T-HALF (h) Mean (S.D.)	2.69 (0.45)	2.78 (0.44)

Reviewer's comment:

- The 40 mg tablet are to be bioequivalent to a dosing of 2x 20 mg capsules.
- PK parameters for the main metabolite BMS-510849 are comparable.

Relative bioavailability study CV 181021

Title:

“Study Of The Bioavailability Of Bms-477118 Administered As 1 X 5 Mg Tablet Relative To Bms-477118 Administered As 1 X 5 Mg Capsule In Healthy Subjects”

Objective:

To assess the bioavailability of saxagliptin administered in 1 x 5 mg tablet relative to saxagliptin administered in 1 x 5 mg capsules.

Batches used:

Reference product (Treatment A):

- 2 x 20 mg capsule, Product Identification Number BMS-477118-R005-002, Formulation: BMS-477118-08 Capsule

Test product (Treatment B):

- 1 x 40 mg tablet, Product Identification Number: BMS-477118-K005-106, Formulation: BMS-477118-11 film coated tablet

Results:

Figure 5 Mean (+ SD) plasma concentration-time profiles for saxagliptin (BMS-477118, left) and BMS-510849 (right) following administration of a single oral 1 x 5 mg dose of saxagliptin as a tablet (n=15, -○-) or 1 x 5 mg dose of saxagliptin as capsule (n=15, -■-)

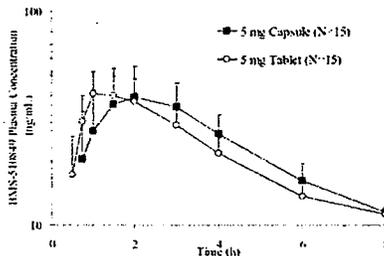
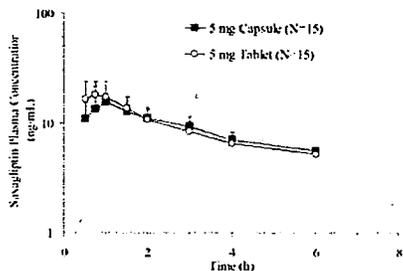


Table 7 Results of Statistical analyses on saxagliptin pharmacokinetic parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		Tablet/Capsule Ratio of Adjusted Geometric Means	
	Saxagliptin 1 x 5 mg Capsule	Saxagliptin 1 x 5 mg Tablet	Point Estimate	90% C.I.
C _{max} (ng/mL)	15	18	1.19	(0.99, 1.42)
AUC(INF) (ng/mL·h)	65	66	1.02	(0.93, 1.11)
AUC(0-T) (ng/mL·h)	35	42	1.20	(1.12, 1.29)

Table 8 Results of Statistical analyses on BMS-510849 pharmacokinetic parameters

Pharmacokinetic Parameter	Treatment	
	Saxagliptin 1 x 5 mg Capsule (n=15)	Saxagliptin 1 x 5 mg Tablet (n=15)
C _{max} (ng/mL) Geometric Mean (C.V. %)	41 (35)	42 (24)
AUC(INF) (ng/mL·h) Geometric Mean (C.V. %)	214 (20) ^a	204 (21) ^a
AUC(0-T) (ng/mL·h) Geometric Mean (C.V. %)	139 (38)	144 (29)
T _{max} (h) Median (Min. Max)	1.98 (0.98, 2.98)	1.48 (0.98, 2.02)
T-HALF (h) Mean (S.D.)	2.68 (0.79) ^a	2.60 (0.37) ^a

Reviewer's comment:

- The tablet formulation meets the bioequivalence criteria for AUC_{inf} and but is outside the 80-125% boundaries for the 90% confidence interval in regards to C_{max} and AUC_{0-t}.
- PK parameters of the main metabolite BMS510849 are comparable.

Relative bioavailability study CV 181036

Title:

“Study Of Bioavailability Of Saxagliptin Administered As 1 X 10 Mg Tablet Relative To Saxagliptin Administered As 2 X 5 Mg Tablets In Healthy Subjects”

Objective:

To assess the bioavailability of saxagliptin administered in 1 x 10 mg tablet relative to saxagliptin administered in 2 x 5 mg tablets.

Batches used:

Reference product (Treatment A):

- 2 x 5 mg capsule, Product Identification Number BMS-477118-R005-111,

Test product (Treatment B):

- 1 x 10 mg tablet, Product Identification Number: BMS-477118-K010-122,

Results:

Figure 7 Mean (+ SD) plasma concentration-time profiles for saxagliptin (BMS-477118, left) and BMS-510849 (right) following administration of a single oral 1 x 10 mg dose of saxagliptin as a tablet (n=12, -◆-) or 2 x 5 mg dose of saxagliptin as tablets (n=12, -◇-)

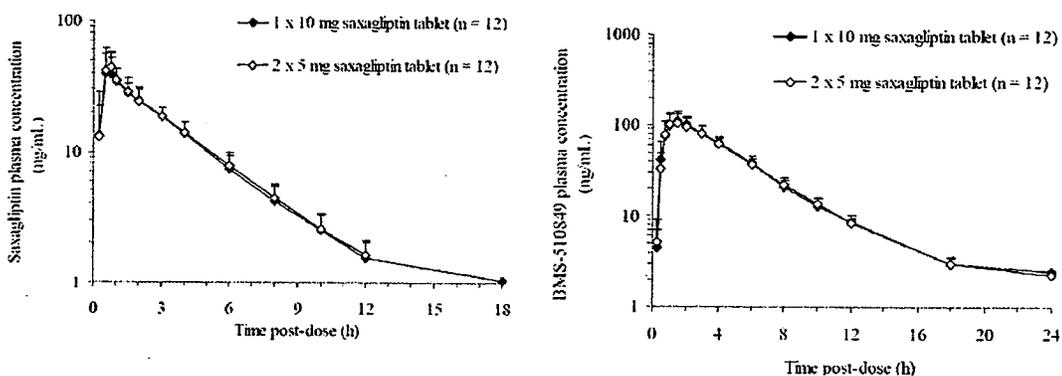


Table 9 Results of Statistical analyses on saxagliptin pharmacokinetic parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		B/A Ratio of Adjusted Geometric Means	
	A	B	Point Estimate	90% C.I.
C _{max} (ng/mL)	45	45	1.00	(0.86, 1.17)
AUC(INF) (ng/mL·h)	141	138	0.97	(0.91, 1.05)
AUC(0-T) (ng/mL·h)	135	132	0.98	(0.91, 1.05)

Table 10 Results of Statistical analyses on BMS-510849 pharmacokinetic parameters

Pharmacokinetic Parameter	Treatment	
	A (n=12)	B (n=12)
C_{max} (ng/mL)		
Geometric Mean (CV %)	110 (23)	113 (27)
AUC(INF) (ng/mL·h)		
Geometric Mean (CV %)	554 (17)	558 (19)
AUC(0-T) (ng/mL·h)		
Geometric Mean (CV %)	539 (17)	543 (19)
T_{max} (h)		
Median (Min. Max)	1.50 (1.00, 2.00)	1.50 (0.75, 2.00)
T-HALF (h)		
Mean (SD)	3.46 (0.37)	3.68 (0.48)

Reviewer's comment:

- The tablet formulation meets the bioequivalence criteria for AUC_{inf}, C_{max} and AUC_{0-t}.
- PK parameters of the main metabolite BMS510849 are comparable.

Analytical Method Validation

The active moieties were measured in human k₃EDTA plasma or urine using liquid chromatography/tandem mass spectrometry, after online extraction and turboionspray ionization. The API was operated in multiple reaction monitoring mode, for the detection of drug and metabolite and their respective internal standards.

For later studies the method was switched to an offline extraction method and chromatographic conditions were modified to determine other monohydroxylated metabolites.

An additional evaluation was performed to assess the influence of other monohydroxylated metabolites with the same mass spectral characteristics as BMS-510849 on the pharmacokinetic results. 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.

Results for the submitted validations are reported in the tables below:

Plasma:

Analyte / Parameter	Curve range (ng/mL)	Calibration	%Bias	Quality control (between day)	
		LLOQ (ng/mL)		%CV	%Bias
Method specifics:	TNJS03-024	LC/MS/MS, multiple reaction monitoring, online solid phase extraction (performed			
BMS-477118	5.00-1000	5.00	10 to -15.5%*	1.3 to 3.7%	4.0 to 6.5%
BMS-510849	10.0-2000	10.00	14.8 to -15.4%*	0.3 to 1.6%	2.0 to 4.1%
Method specifics:	DDBS036/477118	LC/MS/MS, multiple reaction monitoring, online solid phase extraction (performed at BMS)			

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BMS-477118	5.00-1000	5.00	-9.2 to 8.7%	0.0 to 1.9%	-3.2 to 3.4%
BMS-510849	10.0-2000	10.0	-10.8 to 9.9%	0.0 to 2.0%	-1.7 to 2.3%
Method specifics:	<i>TNJS05-032b</i>	LC/MS/MS, multiple reaction monitoring, offline solid phase extraction (performed at)			
BMS-477118	1.00 to 100	1.00	-12.0 to 8.4%	0.0 to 9.1%	-0.9 to 7.0%
BMS-510849	2.00 to 200	2.00	-18.0 to 14.5%*	0.0 to 7.6%	-5.6 to 6.0%
Method specifics:	<i>TNJS06-074a</i>	LC/MS/MS, multiple reaction monitoring, offline solid phase extraction (performed at) , changes in chromatographic conditions allow for detection of other monohydroxylated metabolites			
BMS-477118	1.00 to 100	1.00	-7.5 to 6.0%	0.0 to 6.1%	-4.7 to 4.0%
BMS-510849	2.00 to 200	2.00	-14.0 to 18.0%*	0.0 to 3.6%	-3.0 to 6.9%

* deviations above 15% were at LLOQ

Urine:

Analyte / Parameter	Curve range (ng/mL)	Calibration		Quality control (between day)	
		LLOQ (ng/mL)	%Bias	%CV	%Bias
Method specifics:	<i>TNJS03-031</i>	LC/MS/MS, multiple reaction monitoring, online solid phase extraction (performed at)			
BMS-477118	25.0-5000	25.0	-16.1 to 7.9%*	4.5 to 5.1%	1.2 to 3.8%
BMS-510849	50.0-10000	50.0	-14.1 to 14.4%	1.1 to 2.2%	-3.8 to 1.0 %
Method specifics:	<i>DDBS037/477118</i>	LC/MS/MS, multiple reaction monitoring, online solid phase extraction (performed at BMS)			
BMS-477118	25.0-5000	25.00	-9.4 to 8.5%	0.0 to 2.1 %	-1.8 to 4.4%
BMS-510849	50.0-10000	50.0	-12.9 to 13.4%	-0.6 to 7.0 %	0.0 to 4.0%
Method specifics:	<i>TSL05-150</i>	LC/MS/MS, multiple reaction monitoring, offline solid phase extraction (performed at)			
BMS-477118	5.00 to 1250	5.00	-6.6 to 6.6%	0.3 to 7.0 %	-2.5 to 5.3%
BMS-510849	10.0 to 2500	10.0	-6.6 to 10.4%	0.0 to 9.7%	-3.6 to 4.5%
Method specifics:	<i>TNJS06-075</i>	LC/MS/MS, multiple reaction monitoring, offline solid phase extraction (performed at) changes in chromatographic conditions allow for detection of other monohydroxylated metabolites			
BMS-477118	5.00 to 1250	5.00	-7.6 to 11.0	0.0 to 10.2%	-1.8 to 4.6%
BMS-510849	10.0 to 2500	10.0	-10.0 to 11.2	0.0 to 14.8%	-1.8 to 1.0%

* deviations above 15% were at LLOQ

Method validation for assessment of drugs used in DDI studies:

Analyte / Parameter	Calibration			Quality control (between day)	
	Curve range	LLOQ	%Bias	%CV	%Bias
Ketoconazole	0.0500 to 5.00 mcg/mL	0.0500 mcg/mL	-1.57 to 0.663%	2.95 to 5.91%	0.494 to 1.28%
Metformin	10.0 to 5000 ng/mL	10.0 ng/mL	-1.52 to 1.73%	1.20 to 5.17%	-2.08 to 1.07 %
Glyburide	2.00 to 300.60 ng/mL	2.00 ng/mL	-3.04 to 1.84%	3.91 to 5.54%	-2.69 to 1.41%
Pioglitazone	10.20 to 4079.20 ng/mL	10.20 ng/mL	-1.44 to 1.62%	4.81 to 7.74 %	1.87 to 7.46 %
Hydroxyioglitazone	9.91 to 1981.60 ng/mL	9.91 ng/mL	-2.82 to 1.90%	5.32 to 7.98%	-0.05 to 7.40%
Digoxin	0.1 to 20 ng/mL	0.1 ng/mL	-3.3 to 4.0%	4.1 to 10.3%	-5.3 to 3.8%
Simvastatin	0.150 to 60.0 ng/mL	0.0150 ng/mL	-2.0 to 2.3%	1.0 to 3.4%	-6.3 to 1.7%
Simvastatin acid	0.0500 to 1.0. ng/mL	0.0500 ng/mL	-2.6 to 3.0%	0.9 to 7.4%	-5.3 to 9.0%
Diltiazem	2.029 to 20294.816 ng/mL	0.101 ng/mL	-1.98 to 3.63	2.76 to 8.72%	-5.08 to -0.07%

4.3 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

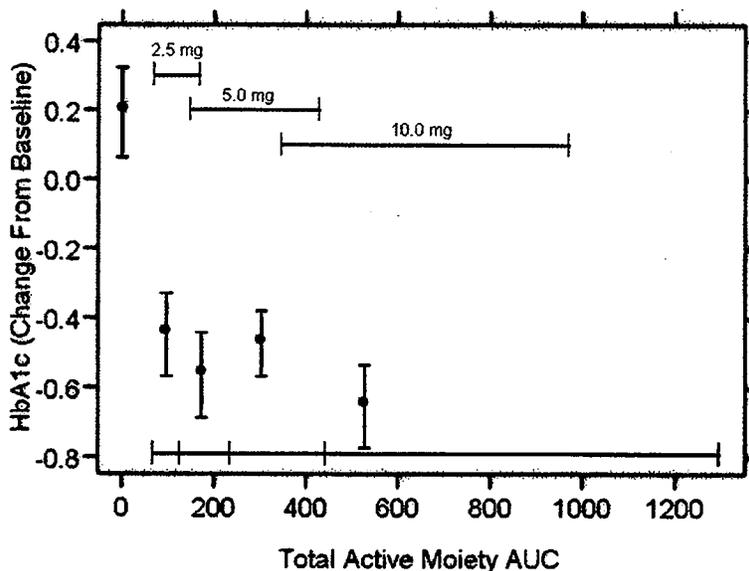
The purpose of this review is to address the following key questions.

1.1.1 Do the exposure-response relationships for effectiveness and safety support the proposed fixed doses of saxagliptin, 2.5 and 5 mg?

The sponsor's proposed doses are acceptable based on this reviewer's exposure-response analysis for effectiveness and safety.

Changes in efficacy above the 5 mg are not significant (Figure 1). The 5 mg dose shows improved reduction when compared to the 2.5 mg dose only prior to 24 weeks.

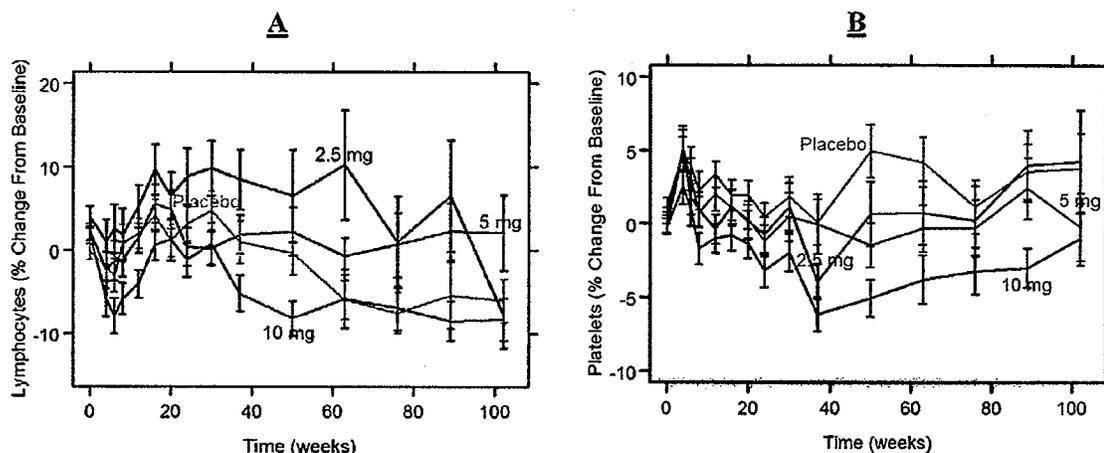
Figure 1. Exposure-Response Relationship for HbA1c Change from Baseline at Week 24. Mean HbA1c change from baseline for each quartile of exposures (AUC) are plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety 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.



Safety of the 5 mg dose is acceptable. While exposures in the 10 mg dose show reduced platelet (5%) and lymphocyte (4%) counts (Figure 2) this drop has not yet been

determined to be clinically significant. It may be of interest to dose 2.5 mg saxagliptin in patients where protecting the lymphocyte or platelet count is critical to patient care.

Figure 2. Time-course of lymphocyte (Panel A) and platelet (Panel B) response by dose. Data and error bars are plotted as mean \pm SEM.



Creatinine clearance showed no difference before and after long term treatment with saxagliptin.

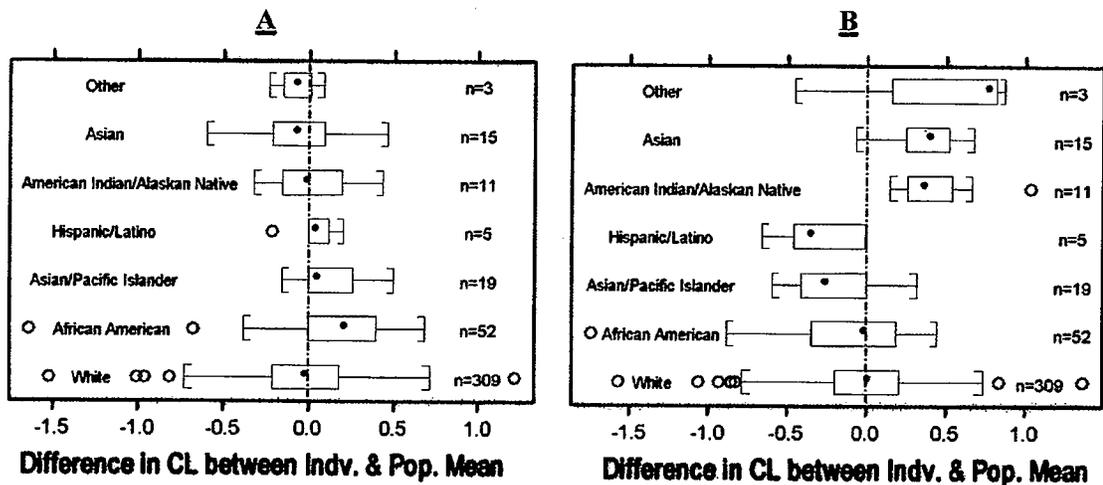
1.1.2 Are there intrinsic and/or extrinsic factors that influence the pharmacokinetics of saxagliptin enough that dose adjustment should be recommended?

The Pharmacometrics division of the Office of Clinical Pharmacology has reviewed the sponsor's population pharmacokinetic analysis and found their methods and results to be acceptable.

Renal function was confirmed to be an important determinant of the elimination of saxagliptin.

The sponsor used race to better predict the clearance of the metabolite. This was confirmed by checking each race category against the change in clearance from the population mean (Figure 3, Panel B). This raised the question whether race influenced saxagliptin's clearance. Saxagliptin clearance was plotted against the change in clearance from the population mean also (Figure 3, Panel A). However for saxagliptin, there was no apparent difference across races.

Figure 3. Race does not influence saxagliptin clearance (Panel A) but does determine the clearance of the metabolite (Panel B). Distributions of the individual's difference from the population mean are plotted for each race category. The number in each group is indicated by "n" on the right side of the graph.



1.1.3 Is the proposed labeling regarding the dosing of saxagliptin adequate?

The proposed label was written thoroughly and the pharmacokinetic content is accurate. Minimal changes have been made to remove unnecessary or promotional content from the label.

1.2 Recommendations

The office of clinical pharmacology has reviewed this application and found the saxagliptin NDA acceptable.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

~~Labeling statements to be removed are shown in red strikethrough font and suggested labeling to be included is shown in underline blue font.~~

~~Labeling statements to be removed are shown in red strikethrough font and suggested labeling to be included is shown in underline blue font.~~

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3 Page(s) Withheld

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

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

2 RESULTS OF SPONSOR'S ANALYSIS

The results of sponsor's analysis are summarized below.

2.1 Exposure Response Models for Effectiveness and Safety:

The sponsor conducted an exposure-response analysis for their primary efficacy endpoint and for three biomarkers unrelated to efficacy (lymphocytes, platelets, and creatinine clearance). The following sections describe the results of each exposure-response modeling analysis. Simulation was done to estimate the efficacy and safety following 6 mo. of therapy in phase III clinical trials.

Exposure-Efficacy Response Analyses: A1C

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) %.

Exposure-Safety Analyses: Absolute Lymphocyte Counts, Platelet Counts, and Serum Creatinine Concentration

The exposure-safety 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.

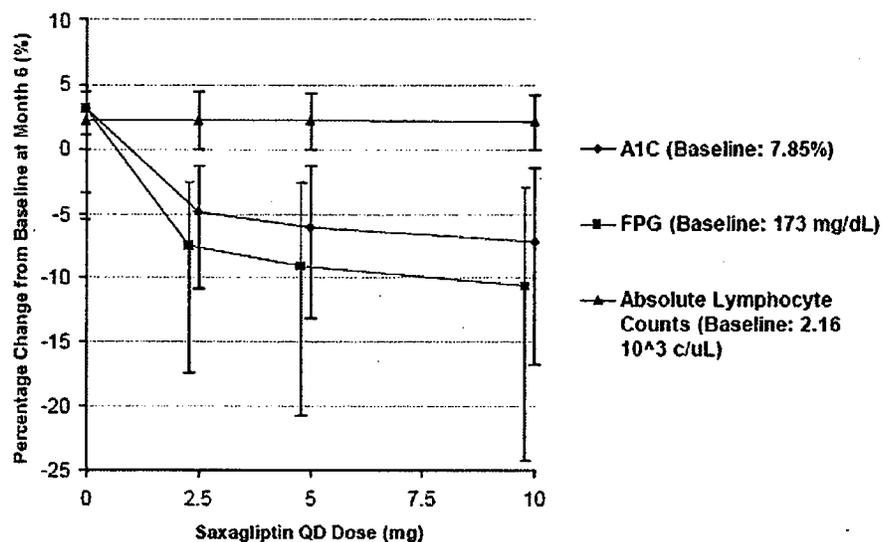
Exposure-safety modeling did not find a model that could relate the platelet counts and serum creatinine concentration to the total active moiety exposure after 6 months of saxagliptin administration at QD doses of 2.5, 5, and 10 mg. It was concluded that the responses of platelet counts and serum creatinine 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.

Model-Predicted Efficacy and Safety Outcomes after 6 Months of Saxagliptin Treatment

Base on the results of the population pharmacokinetic and exposure-response analyses, the population expected 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 4. 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 4. Model Predicted Efficacy and Safety Outcomes after 6 Months of Saxagliptin Treatment. Solid symbols and vertical bars represent the median and 95% prediction intervals.



Source: Sponsor's Figure S1 in population PK report on page 7.

2.2 Population Pharmacokinetic Analysis:

The sponsor tested whether intrinsic factors such as age, gender, body weight, body mass index, or race and extrinsic factors such as administration with a meal influence saxagliptin and BMS-510849 pharmacokinetics through population pharmacokinetic modeling. The following summarizes their results of this analysis and the salient factors that influenced the kinetics.

Population Pharmacokinetic Analyses: Saxagliptin and BMS-510849

The population PK (PPK) of saxagliptin was characterized by a 2-compartment model with first order absorption and linear clearance. Modeling BMS-510849 plasma concentration was performed by conditioning on the predicted saxagliptin concentration from the posterior Bayesian estimates of individual saxagliptin parameters. The PPK of BMS-510849 plasma concentration was characterized by a 2-compartment model with linear clearance.

The parameter estimates for the final exposure models of saxagliptin and BMS-510849 are presented in Table 11 and Table 12, respectively. The fraction of metabolism from saxagliptin dose to BMS-510849, a scaling factor in parent/metabolite modeling, was fixed to 35.8%. The typical values (model estimated geometric means) and standard errors of these model parameters are presented in the Fixed-Effects section of Table 11 and Table 12.

Inter-individual variability (IIV) was estimated on CL/F , $V2/F$, Ka , CLM/F , and $V2M/F$. The IIV in these parameters was described by log-normal IIV models, the estimated

variances of which are presented in the Random-Effects section of Table 11 and Table 12, along with the estimated covariance between CL/F and $V2/F$, and between CLM/F and $V2M/F$.

The residuals for saxagliptin and BMS-510859 were each described by a proportional model for clinical pharmacology studies, and a combined proportional and additive model for the Phase 3 study. The standard deviation of these error terms are given in the Residual-Error section of Table 11 and Table 12.

Table 11. Saxagliptin Population Pharmacokinetic Parameter Estimates

Name ^{a,b} [Units]	Symbol	Estimate ^c	Standard Error (RSE%) ^d	95% Confidence Interval ^e
Fixed Effects				
K_A [1/hr]	θ_1	0.776	0.0990 (12.8)	0.582 - 0.970
CL/F [L/hr]	θ_2	45.3	0.935 (2.06)	43.5 - 47.1
$V2/F$ [L]	θ_3	151	3.19 (2.11)	145 - 157
$V3/F$ [L]	θ_4	53.8	14.2 (26.4)	26.0 - 81.6
Q/F [L/hr]	θ_5	5.74	0.405 (7.06)	4.95 - 6.53
$BSA-V2/F$	θ_8	0.448	0.0539 (12.0)	0.342 - 0.554
$CRCL2-CL/F$	θ_9	1.23	0.142 (11.5)	0.952 - 1.51
$FED-K_A$	θ_{10}	-0.995	0.158 (15.9)	-1.30 - -0.685
Random Effects				
ZKA	$\omega_{1,1}$	0.635 (0.797)	0.0781 (12.3)	0.482 - 0.788
ZCL	$\omega_{2,2}$	0.0732 (0.271)	0.0164 (22.4)	0.0411 - 0.105
$ZV2$	$\omega_{3,3}$	0.0597 (0.244)	0.00987 (16.5)	0.0404 - 0.0790
$ZCL:ZV2$	$\omega_{2,3}$	0.0565 (0.855)	0.0115 (20.4)	0.0340 - 0.0790
Residual Error				
$ZPROP.no.011$	$\sigma_{1,1}$	0.0911 (0.302)	0.00560 (6.15)	0.0801 - 0.102
$ZPROP.011$	$\sigma_{2,2}$	0.0698 (0.264)	0.00594 (8.51)	0.0582 - 0.0814
$ADD.011$ [ng/mL]	$\sigma_{4,4}$	3.48 (1.87)	0.933 (26.8)	1.65 - 5.31

^a $BSA-V2/F$, $CRCL2-CL/F$, and $FED-K_A$ are the parameters for the covariate impact on PPK structural parameters. See Appendix 5.1.1.2B for function formats of these parameters

^b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

^c Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

^d RSE% is the relative standard error (Standard Error as a percentage of Estimate)

^e Confidence intervals of Random Effects and Residual Error parameters are for *Variance or Covariance*

Source: Sponsor's Table S1 in population PK report on page 4.

Table 12. Population Pharmacokinetic Parameter Estimates for BMS-510849.

Name ^{a,b} [Units]	Symbol	Estimate ^c	Standard Error (RSE%) ^d	95% Confidence Interval ^e
Fixed Effects				
CLM/F [L/hr]	θ_1	7.89	0.182 (2.31)	7.53 - 8.25
QM/F [L/hr]	θ_2	1.02	0.0884 (8.67)	0.847 - 1.19
V2M/F [L]	θ_3	4.23	0.307 (7.26)	3.63 - 4.83
V3M/F [L]	θ_4	5.11	0.160 (3.13)	4.80 - 5.42
CRCL-CLM/F	θ_5	0.444	0.0677 (15.2)	0.311 - 0.577
BWT-CLM/F	θ_6	0.656	0.133 (20.3)	0.395 - 0.917
RACE-CLM/F	θ_7	-0.304	0.0514 (16.9)	-0.405 - -0.203
BWT-V2M/F	θ_{10}	0.719	0.153 (21.3)	0.419 - 1.02
Random Effects				
ZCLM	$\omega_{1,1}$	0.156 (0.395)	0.0173 (11.1)	0.122 - 0.190
ZV2M	$\omega_{2,2}$	0.218 (0.467)	0.0358 (16.4)	0.148 - 0.288
ZCLM-ZV2M	$\omega_{1,2}$	0.0824 (0.447)	0.0177 (21.5)	0.0477 - 0.117
Residual Error				
ZPROP.no.011	$\sigma_{1,1}$	0.0944 (0.307)	0.00514 (5.44)	0.0843 - 0.104
ZPROP.011	$\sigma_{2,2}$	0.0587 (0.242)	0.00476 (8.11)	0.0494 - 0.0680
ADD.011 [ng/mL]	$\sigma_{3,3}$	2.81 (1.68)	0.676 (24.1)	1.49 - 4.13
ZPROP.no.011.Me t	$\sigma_{4,4}$	0.102 (0.319)	0.00681 (6.68)	0.0887 - 0.115
ZPROP.011.Met	$\sigma_{5,5}$	0.0687 (0.262)	0.00655 (9.53)	0.0559 - 0.0815
ADD.011.Met [ng/mL]	$\sigma_{6,6}$	7.29 (2.70)	2.54 (34.8)	2.31 - 12.3

^a CrCL-CLM/F, BWT-CLM/F, RACE-CLM/F, and BWT-V2M/F are the parameters for the covariate impact on PPK structural parameters. See Appendix 5.2.1.2B for the function format of these parameters.

Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

^b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

^c Random Effects and Residual Error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and Covariance (Correlation) for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

^d RSE% is the relative standard error (Standard Error as a percentage of Estimate)

^e Confidence intervals of Random Effects and Residual Error parameters are for Variance or Covariance

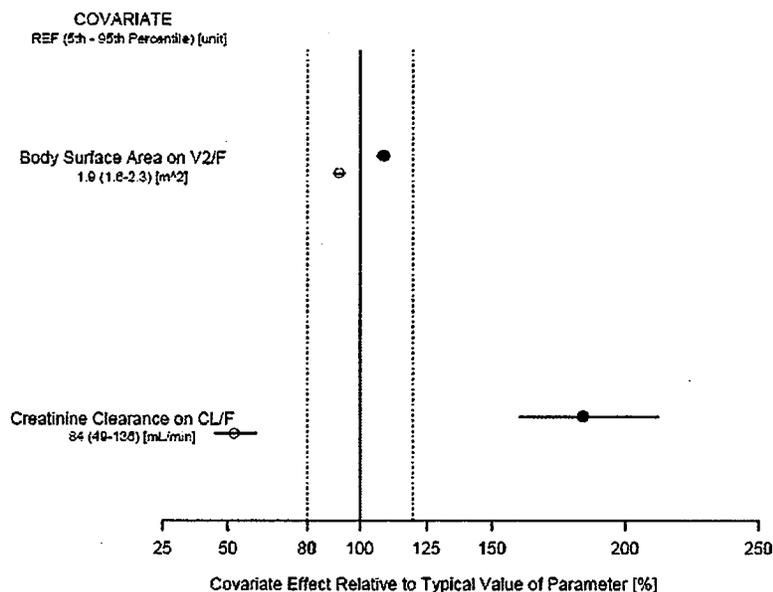
Source: Sponsor's Table S2 in population PK report on page 5.

Saxagliptin Covariate Effects

Graphical representations of the covariate effects in the covariate model are provided in Figure 5 and Figure 6. They show the estimated effect over the range of the covariates, relative to their reference values. The point estimates of the covariate effects at the 5th and 95th percentiles of the covariates values are denoted by the open and closed circles respectively in the figure.

Figure 5. Saxagliptin Population Pharmacokinetic Covariate Model: Effect of Continuous Covariates on Saxagliptin PK Parameters. The solid line represents the typical parameter value and the dotted lines are $\pm 20\%$ the typical value. The sponsor used these reference lines a test to denote

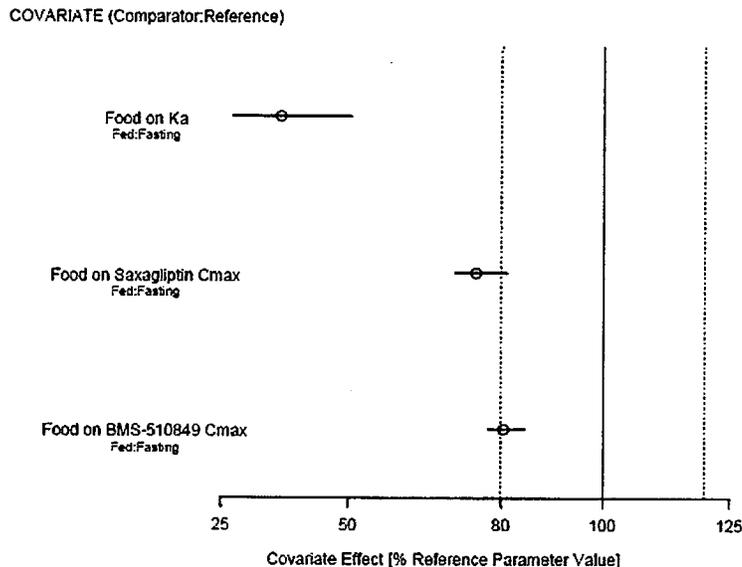
covariates with a significant effect. Those covariates that cause a shift in the 95% CI for the parameter outside of the 20% reference lines are considered statistically different. Whereas when both 95% CI for the adjusted model with the covariate lie within these lines, it is considered there is no difference with the covariate in the model.



Source: Sponsor's Figure 5.1.1.2J in population PK report on page 115.

Figure 5 shows the estimated effect over the range of the continuous covariates, relative to their reference values. Among them, the effect of body surface area is within the range of 80-120% of the reference effects, indicating the low likelihood of being clinically relevant. The effect of creatinine clearance on the apparent clearance from the central compartment of clearance ranges approximately from 50-200% of the reference value. As the steady state exposure is dictated by dose and clearance, this suggests the exposure of saxagliptin could potentially get doubled in subjects with creatinine clearance of 49 mL/min, the 5th percentile of creatinine clearance in the analysis dataset, comparing to those of subjects with median creatinine clearance of 84 mL/min. The clinical relevance of this finding should be considered when making saxagliptin dosage recommendation.

Figure 6. Saxagliptin Population Pharmacokinetic Covariate Model: Effect of Categorical Covariates on Saxagliptin and BMS-510849 Pharmacokinetic Parameters. The solid line represents the typical parameter value and the dotted lines are $\pm 20\%$ the typical value. The sponsor used these reference lines a test to denote covariates with a significant effect. Those covariates that cause a shift in the 95% CI for the parameter outside of the 20% reference lines are considered statistically different. Whereas when both 95% CI for the adjusted model with the covariate lie within these lines, it is considered there is no difference with the covariate in the model.



Source: Sponsor's Figure 5.1.1.2K in population PK report on page 116.

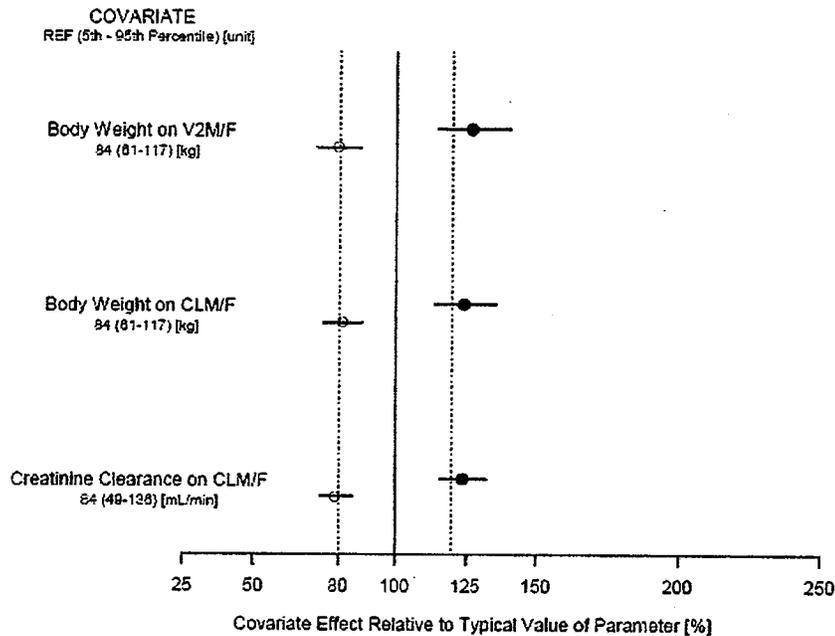
Figure 6 shows the estimated food effect (fed vs. fasting) on K_a , relative to K_a at fasting. The effect of food on the PK of saxagliptin administered as capsule or oral solution is included as a covariate in the exposure modeling.

The covariates that were identified as statistically significant are included in the saxagliptin Final Model: body surface area on the apparent volume of distribution of the central compartment, creatinine clearance on the apparent clearance, and food on the absorption rate constant. All three were considered to be physiologically plausible.

BMS-510849 Covariate Effects

Graphical representations of the covariate effect in the covariate model are provided in Figure 7 and Figure 8. They present the estimated effect of covariates on the corresponding PPK parameters for BMS-510849, over the range of the covariates and relative to their reference values. The point estimates of the covariate effect at the 5th and 95th percentiles of the covariates values are denoted by the open and closed circles, respectively in the figure.

Figure 7. BMS-510849 Population Pharmacokinetic Covariate Model: Effect of Continuous Covariates on BMS-510849 Pharmacokinetic Parameters. The solid line represents the typical parameter value and the dotted lines are $\pm 20\%$ the typical value. The sponsor used these reference lines a test to denote covariates with a significant effect. Those covariates that cause a shift in the 95% CI for the parameter outside of the 20% reference lines are considered statistically different. Whereas when both 95% CI for the adjusted model with the covariate lie within these lines, it is considered there is no difference with the covariate in the model.

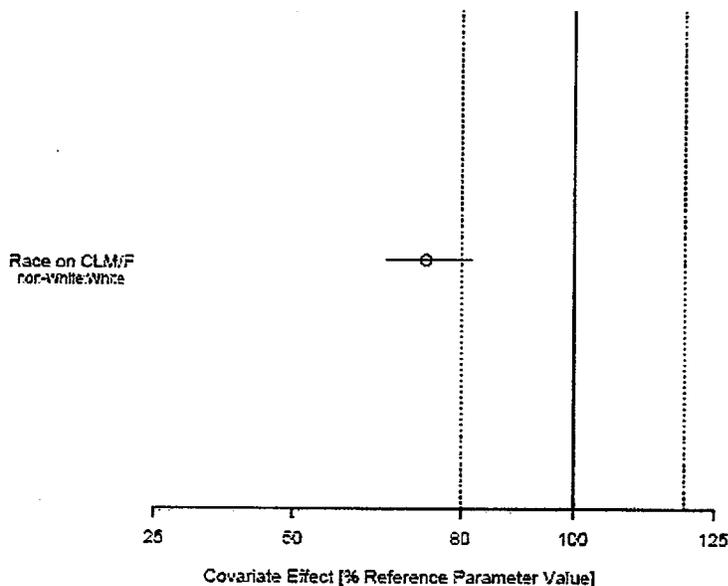


Source: Sponsor's Figure 5.2.1.2J in population PK report on page 144.

Figure 7 shows the estimated effect of covariates on the corresponding PPK parameters for BMS-510849, over the range of the continuous covariates and relative to their reference values. The estimated effect is generally within 75-140%.

Figure 8. BMS-510849 Population Pharmacokinetic Covariate Model: Effect of Categorical Covariates on BMS-510849 Pharmacokinetic Parameters. The solid line represents the typical parameter value and the dotted lines are $\pm 20\%$ the typical value. The sponsor used these reference lines a test to denote covariates with a significant effect. Those covariates that cause a shift in the 95% CI for the parameter outside of the 20% reference lines are considered statistically different. Whereas when both 95% CI for the adjusted model with the covariate lie within these lines, it is considered there is no difference with the covariate in the model.

COVARIATE (Comparator:Reference)



Source: Sponsor's Figure 5.2.1.2K in population PK report on page 145.

Figure 8 shows the estimated effect of race (non-White vs. White) on the estimated typical value of apparent clearance from central compartment, CLM/F for BMS-510849. The effect of race on the PK of BMS-510849 was included as a covariate in the exposure model. In the PPK analysis dataset, there were 309 White subjects and 105 non-White subjects, consisting of 6 race groups). The number of subjects in each race group is not sufficient to examine the effect for each race group. All non-White subjects were therefore grouped together and their estimated CLM/F was compared with that of White subjects. Figure 8 shows that non-White group's estimated CLM/F is about 76% of that of White group. However, caution has to be exerted when interpreting the race effect, as the different races within the bundled non-White group may not have the same PK characteristics.

Four identified statistically significant covariates are included in the final model: body weight on the apparent volume of distribution of the central compartment, and creatinine clearance, body weight, and race (Non-White vs. White) on the apparent clearance from the central compartment. All of these covariates are considered to be physiologically plausible, but the magnitude of their impact on the corresponding PPK parameters for BMS-510849 is small.

2.3 Sponsor's Conclusions:

Using data collected from 4 clinical pharmacology studies and 1 Phase 3 monotherapy study, the population-based modeling analyses for quantifying the systemic exposures of saxagliptin and BMS-510849 and the exposure-response relationship for efficacy and safety after 6 months of saxagliptin administration, led to the following conclusions:

- The PK of saxagliptin and BMS-510849 can each be described adequately by a 2-compartment linear model with no time-variant parameters. The exposure

modeling analyses do not recommend saxagliptin dosage adjustment on the basis of body weight, gender, and age alone in adult subjects, but suggest taking renal function into consideration for saxagliptin dosing recommendation.

- The reduction of glycosylated hemoglobin level and fasting plasma glucose concentration are linearly related to the log of the total active moiety exposure after 24 weeks of saxagliptin administration at QD doses of 2.5, 5, and 10 mg.
- The platelet counts and serum creatinine concentration are found not to be related to the total active moiety exposure after 6 months of saxagliptin administration at QD doses of 2.5, 5, and 10 mg. The reduction of absolute lymphocyte counts is linearly related to the increase of total active moiety exposure within the tested QD dose range of 2.5 to 10 mg, but the magnitude of the change, approximately 4% placebo-adjusted decrease for subjects receiving saxagliptin 5 mg QD treatment for 6 months, is unlikely to be clinically relevant.

Reviewer's Comments on Sponsor's Analysis:

The sponsor provided labeling statements relevant to intrinsic and extrinsic factors that alter the pharmacokinetics and dosing of saxagliptin. The pharmacokinetics of saxagliptin were evaluated to determine the accuracy of these statements and whether other critical points need to be stated in the label.

The sponsor also evaluated exposure-response relationships for the primary efficacy endpoint, HbA1c concentrations in blood, and three safety endpoints, lymphocyte count, platelet count, and creatinine clearance. These relationships were evaluated to determine if 1) drug exposure supports drug efficacy and 2) whether the safety response is acceptable at the observed or highest predicted exposures. No other critical safety signals were observed at the clinically relevant exposures.

3 REVIEWER'S ANALYSIS

3.1 Objectives

Analysis objectives are:

1. To determine the major intrinsic factors (age, gender, body weight, creatinine clearance, race) and extrinsic factors (administration with food) that influence the pharmacokinetics of saxagliptin and its active metabolite (BMS-510849).
2. To use the results from the first objective to validate the accuracy of the label statements made by the sponsor and to include additional relevant information if necessary.
3. To evaluate the sponsor's exposure response models and determine the extent to which drug exposure supports efficacy of saxagliptin and the extent that safety biomarkers are influenced by clinically relevant concentrations.

3.2 Methods

3.2.1 Data Sets

Data sets used are summarized in Table 13.

Table 13. Analysis Data Sets

Study Number	Name	Link to EDR
Pop PK Report	hba1c.xpt	\\Cdsub1\evsprod\NDA022350\0000\m5\datasets\poppk\analysis
Pop PK Report	lym.xpt	\\Cdsub1\evsprod\NDA022350\0000\m5\datasets\poppk\analysis
Study 011	c1lab01.xpt, c1lab02.xpt, c1lab03.xpt	\\Cdsub1\evsprod\NDA022350\0000\m5\datasets\cv181011\analysis\st

3.2.2 Software

NONMEM VI was used to review the sponsor's pharmacokinetic analysis. S-plus was used to for all linear regressions and plots of the exposure response relationships for efficacy and safety.

3.3 Results

3.3.1 Do the exposure-response relationships for effectiveness and safety support the proposed fixed doses of saxagliptin, 2.5 and 5 mg?

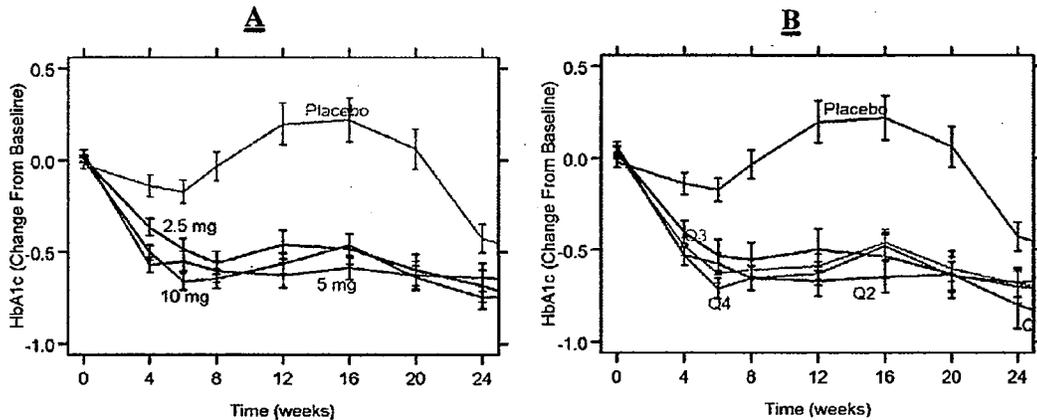
3.3.1.1 Effectiveness

Figure 1 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. The 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.

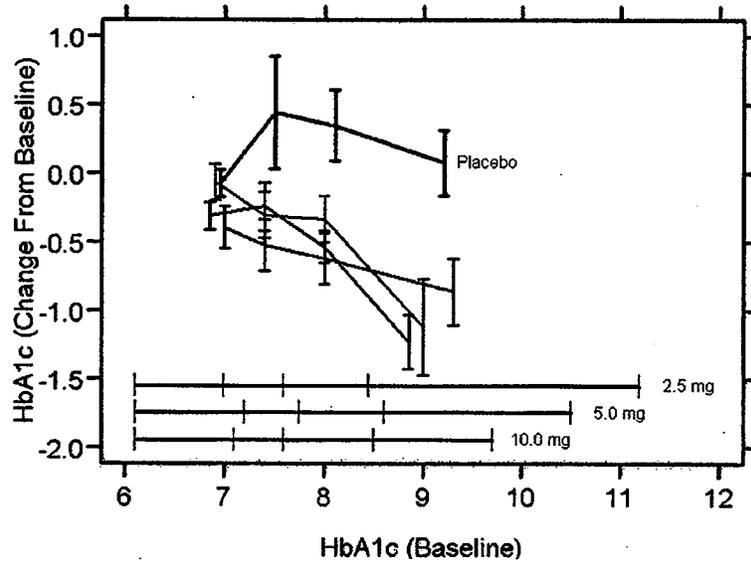
Efficacy of saxagliptin was monitored at various weeks over the duration of the phase 3 clinical trials. In study 11 subjects received either placebo, 2.5, 5, or 10 mg of saxagliptin for 24 weeks. Figure 9 shows 1) there is no dose-response for effectiveness in study 11 above the 2.5 mg dose (Panel A) and 2) 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 9. 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 1 or Figure 9. Reduction in HbA1c is greater for 5 mg than 2.5 mg saxagliptin as early as 12 weeks. If it is important to reduce HbA1c quickly, 5 mg is superior to 2.5 mg saxagliptin. However, change from baseline in HbA1c at week 24 is the primary endpoint and no difference between 2.5-, 5-, and 10-mg doses were observed at this time point in Figure 1 or Figure 9.

Figure 10. Greater Reduction in HbA1c is observed for Higher Baseline HbA1c concentrations at week 24.

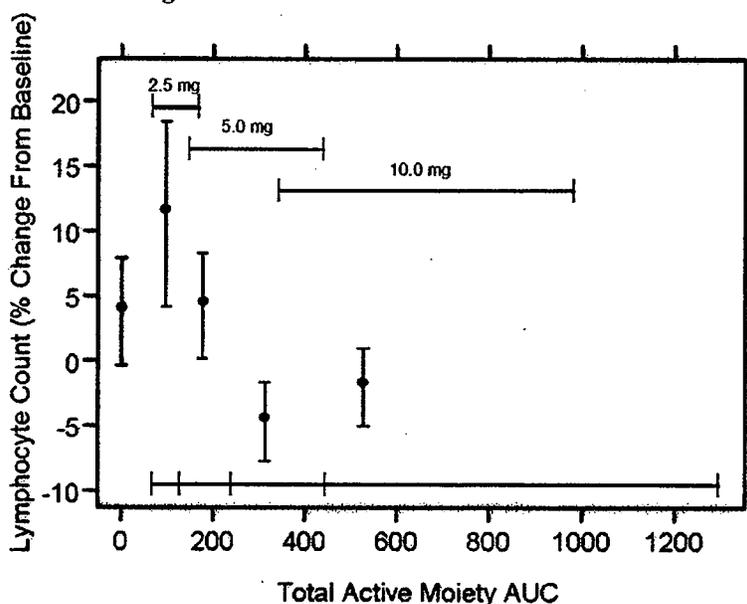


Of interest is that the magnitude of the response can be correlated to the extent of the disease (Figure 10). Patients with higher HbA1c concentrations are likely to have a greater reduction in response than patients with close to normal HbA1c concentrations. While this finding has relevance for the expected response, dosing amounts greater than 2.5 mg at the same baseline is not expected to increase the reduction in HbA1c at 24 weeks.

3.3.1.2 Safety

The sponsor's proposed doses (2.5 and 5 mg) are acceptable from a safety point of view. Lymphocyte count, platelet count, and serum creatinine concentrations were plotted to examine for correlation with saxagliptin exposure (Figure 11, Figure 13, and Figure 15).

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.



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. The question then arises what will happen after 24 weeks? Will the lymphocyte count continue to drop? Figure 12 shows 1) there appears to be a dose dependent response and 2) 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. Starting at the 2.5 mg dose and increasing to 5 mg if necessary may be a safer regimen if lymphocyte count is of concern.

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.

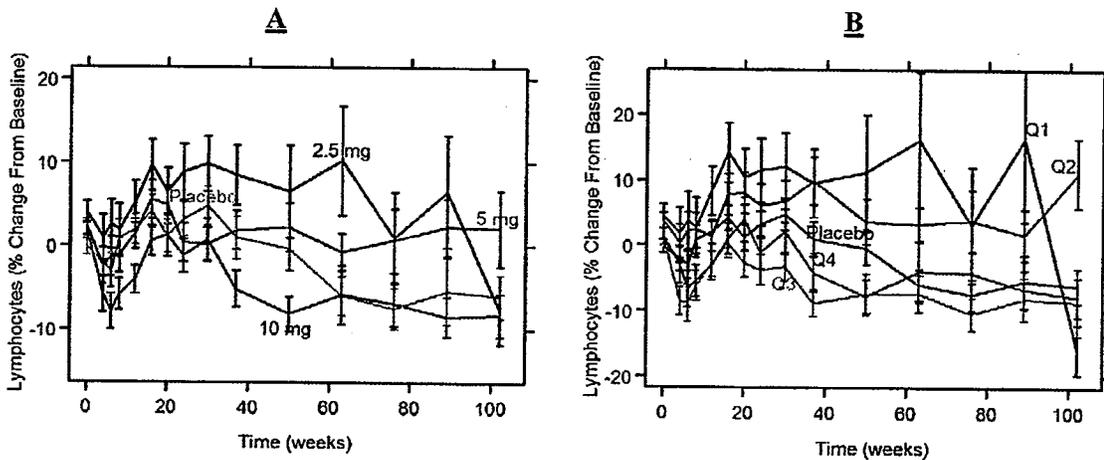
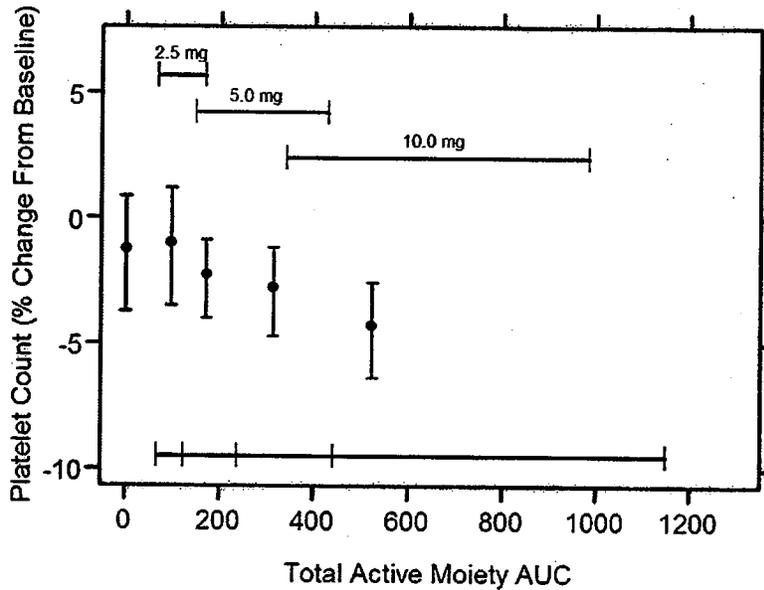


Figure 13. Exposure-Response Relationship for Platelet Count. Mean change from baseline in platelet count for each quartile of exposures (AUC) is plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety for each dose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



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. However, does the reduction at the same dose for 52, 78, or 104 weeks continue to increase? Figure 14 confirms that there are both dose- and exposure-response relationships for saxagliptin treatment and platelet count. At the 5 mg dose (Panel A) there appears to be no change from baseline. Panel B confirms the exposure-response relationship in Figure 13 and

indicates exposures from the 5- and 10-mg doses could reduce platelet count by as much as 5% at week 36. The clinical significance of this change has not been identified. However, if platelet count is of concern, initiating treatment with 2.5 mg saxagliptin is recommended.

Figure 14. Time-course of platelet response by dose (Panel A) and exposure quartile (Panel B). Data and error bars are plotted as mean \pm SEM.

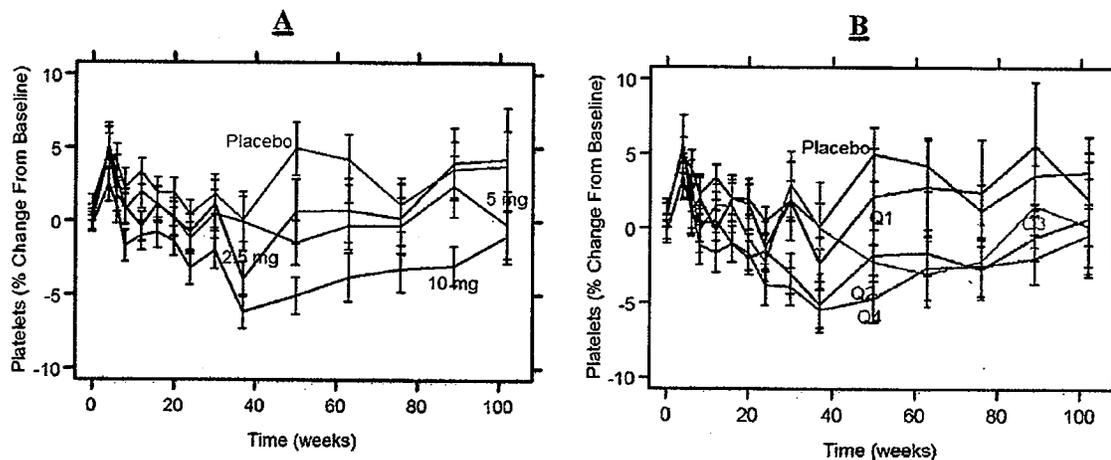
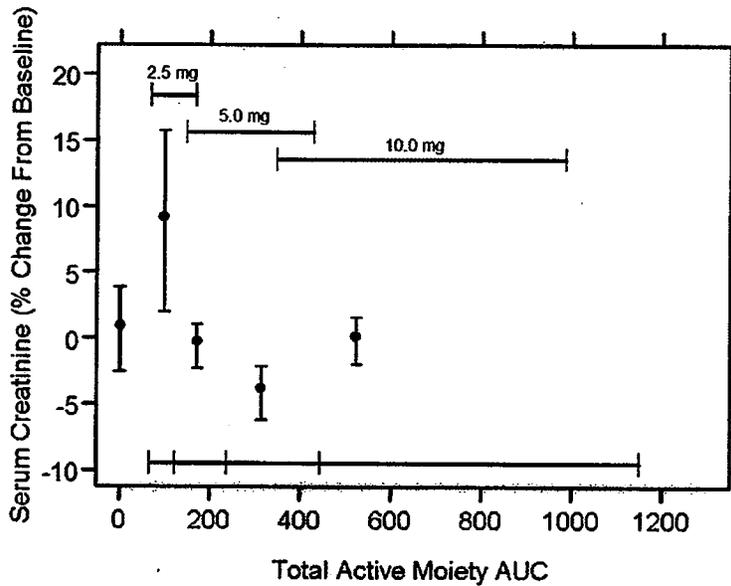


Figure 15. Exposure-Response Relationship for Serum Creatinine. Mean percent change from baseline in serum creatinine for each quartile of exposures (AUC) is plotted \pm SEM. The placebo and treated responses are shown in black and red. The 95% confidence intervals for the AUC for total active moiety 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.



There is no apparent change in serum creatinine in response to saxagliptin exposures (Figure 15). It is not anticipated that increases in saxagliptin exposure will change renal function.

3.3.2 Are there intrinsic and/or extrinsic factors that influence the pharmacokinetics of saxagliptin enough that dose adjustment should be recommended?

The Pharmacometrics division of the Office of Clinical Pharmacology has reviewed the sponsor's population pharmacokinetic analysis and found their methods and results to be generally acceptable.

Figure 16 confirms that saxagliptin's clearance is dependent on renal function. This is in agreement with the sponsor's proposal that reducing the dose from 5 mg to 2.5 mg is necessary for patients with severe renal impairment to maintain exposures observed from the 5 mg dose in patients with normal renal function.

It is not possible to determine the effect of creatinine clearance on clearance of the metabolite. The metabolite is produced and lost in a formation-rate limited manner (i.e. it is lost faster than it is formed). Therefore concentrations in the declining phase of the time-course reflect the formation of the drug rather than the elimination. Only dosing the metabolite alone will indicate whether renal function is directly related to the loss of metabolite.

Figure 16. Saxagliptin clearance is dependent on renal function. Individual clearance estimates are plotted against the individual's baseline creatinine clearance value.

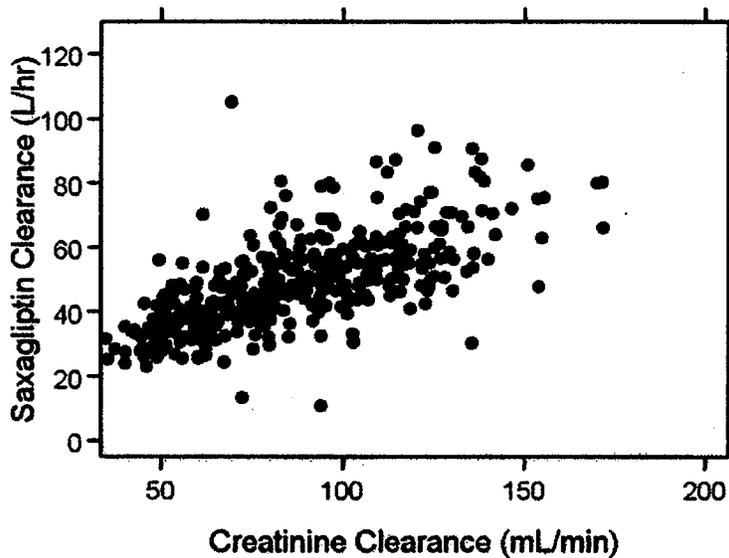
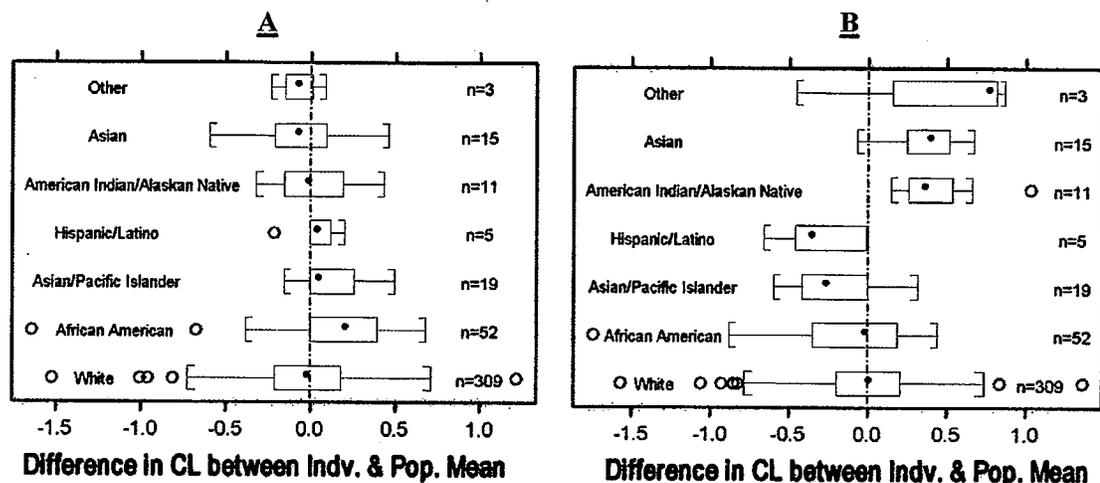


Figure 3, Panel A indicates for saxagliptin that clearance is unchanged across different races. Figure 3, Panel B indicates that metabolite clearance for some of these different race groups is increased (Asian or American Indian/Alaskan Natives) or decreased (Hispanic/Latino) clearance. However, these 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.

3.3.3 Figure 3. Race does not influence saxagliptin clearance (Panel A) but does determine the clearance of the metabolite (Panel B). Distributions of the individual's difference from the population mean are plotted for each race category. The number in each group is indicated by "n" on the right side of the graph.



3.3.4 Is the proposed labeling regarding the dosing of saxagliptin adequate?

The proposed label was written thoroughly and the pharmacokinetic content is accurate. Minimal changes have been made to remove unnecessary content from the label.

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ExposureEfficacyFinal.ssc	Primary Exposure-Response for Effectiveness Code	\Saxagliptin\er\efficacy
MeanTimecourseVsAUCT.ssc	TimeCourse of HbA1c Response by quartile and by dose	\Saxagliptin\er\efficacy
BaselineCov.ssc	Baseline HbA1c effect on Response to Drug	\Saxagliptin\er\efficacy
ExposureSafetyLymphocytes.ssc	Exposure-Response for Lymphocyte Safety Code	\Saxagliptin\er\safety
MeanTimecourseVsAUCT_Lymph.ssc	TimeCourse of Lymphocyte Response by quartile and by dose	\Saxagliptin\er\safety
ExposureSafetyPlatelets.ssc	Exposure-Response for Platelet Safety Code	\Saxagliptin\er\safety
MeanTimecourseVsAUCT_Platlets.ssc	TimeCourse of Platelet Response by quartile and by dose	\Saxagliptin\er\safety
ExposureSafetyCreatinine.ssc	Exposure-Response for Lymphocyte Safety Code	\Saxagliptin\er\safety
Eta1VsCov.ssc	Population PK for Clearance by CRCL and Race	\Saxagliptin\pk

-
- i Saxagliptin and BMS-510849 Population Pharmacokinetic Analyses in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus and Exposure-Response Analyses for Efficacy and Safety in Subjects with Type 2 Diabetes Mellitus. Bristol-Myers Squibb Research and Development; 2008. Document Control No. 930027419 - Section 1.1.1 Pharmacokinetics.
 - ii Bioavailability of BMS-477118 Administered as 1 x 40 mg Tablet Relative to BMS-477118 Administered as 2 x 20 mg Capsules in Healthy Subjects (CV181003). Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930016233.
 - iii Mass Balance and Metabolism of [¹⁴C]BMS-477118 in Healthy Male Subjects (CV181004). Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930017078.
 - iv In Vitro Determination of Protein Binding of BMS-477118 and BMS-510849 in Mouse, Rat, Dog, Monkey and Human Serum. Bristol-Myers Squibb Research and Development; 2008. Document Control No. 930025627.
 - v In Vitro Biotransformation of [¹⁴C]BMS-477118 in Mouse, Rat, Dog, and Human Liver Microsomes, and in cDNA-Expressed Human CYPs (DDBS018/477118). Bristol-Myers Squibb Pharmaceutical Research Institute; 2003. Document Control No. 930004422.
 - vi Investigation of the Enzymes Involved in the In Vitro formation of BMS-510849 from Saxagliptin in Humans, and Kinetics of BMS-510849 Formation. Bristol-Myers Squibb Research and Development; 2007. Document Control No. 930024372.
 - vii Single-Dose Pharmacokinetics and Safety of 10 mg Saxagliptin in Subjects with Hepatic Impairment Compared to Healthy Adult Subjects (CV181020). Bristol-Myers Squibb Research and Development; 2007. Document Control No 930024009.
 - viii Saxagliptin and BMS-510849 Population Pharmacokinetic Analyses in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus and Exposure-Response Analyses for Efficacy and Safety in Subjects with Type 2 Diabetes Mellitus. Bristol-Myers Squibb Research and Development; 2008. Document Control No. 930027419 -

Section 6.1.2 Physiological Covariates on Pharmacokinetics of Saxagliptin and BMS-510849 and Related Population.

- ^{ix} Effects of Age and Gender on the Single Dose Pharmacokinetics of BMS-477118 in Healthy Subjects (CV181018). Bristol-Myers Squibb Pharmaceutical Research Institute; 2006. Document Control No. 930018435.

4.4 OCP Filing Memo

1.1.1 Office of Clinical Pharmacology

2 NEW DRUG APPLICATION FILING AND REVIEW FORM

2.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	22-350	Brand Name	Not Decided
OCP Division	DCP2	Generic Name	Saxagliptin
Medical Division	DMEP	Drug Class	DPP4 Inhibitor
OCP Reviewer	Jayabharathi Vaidyanathan, Ph.D.	Indication(s)	Type 2 diabetes
OCP Team Leader	Sally Choe, Ph.D.	Dosage Form	2.5 mg, 5 mg tablets
		Dosing Regimen	QD
Date of Submission	6/30/08	Route of Administration	Oral
Estimated Due Date of OCPB Review	3/13/09	Sponsor	Bristol-Myers Squibb
PDUFA Due Date	4/30/09	Priority Classification	SI
2.1.1.2 Division Due Date	4/9/09		

2.1.1.2.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X			
Blood/plasma ratio:				
Plasma protein binding:	X	1		(location Pre-clinical module 4)
Pharmacokinetics (e.g., Phase I) -				
2.2 Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
2.2.1 Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				

fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	6		
In-vitro:	X	17		(location Pre-clinical module 4)
Subpopulation studies -				
ethnicity:				
gender:	X	1		
pediatrics:				
geriatrics: (Age)	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:		3		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		67		
2.2.1.1.1				
2.2.1.1.2	Filability and QBR comments			

2.2.1.2	"X" if yes	2.2.1.2.1.1.1.1.1.1 Comments
2.2.1.3 Application filable ?	YES	Reasons if the application is not filable (or an attachment if applicable)
2.2.1.4 Comments sent to firm ?		<ul style="list-style-type: none"> Saxagliptin is a chiral molecule with 4 chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. The sponsor is recommended to address the chiral conversion using a stereo-specific assay for detection of saxagliptin and its isomer.
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1) What is the exposure-response relationship for saxagliptin? 2) What is the effect of saxagliptin on QT interval? 3) Is dosing appropriate in renal and hepatic impaired patients? 4) Is dosing appropriate in elderly patients? 5) What are the possible drug interactions with saxagliptin?
Other comments or information not included above		
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.	
Secondary reviewer Signature and Date	Sally Choe, Ph.D.	

Summary:

Saxagliptin belongs to the class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improves glycemic control in patients with type 2 diabetes by increasing the endogenous levels of the incretin hormones, GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide) by inhibiting the enzyme responsible for their degradation, DPP-4.

The Clinical Pharmacology section consist of 26 studies consisting of the following: ascending dose studies, biopharmaceutical studies, thorough QTc study, drug interaction studies, special population studies (age, gender, renal impairment and hepatic impairment), and population PK analysis. In addition there are 23 bioanalytical study reports, 17 *in vitro* metabolism/permeability studies, and one protein binding study.

The 5 mg dose is being proposed to be administered once daily regardless of food. For moderate or severe renal impairment or end stage renal disease a reduced dose of 2.5 mg is being proposed by the sponsor. No dosage adjustments are being proposed on the basis of age, gender, or race.

The Phase 3 formulation differs from the to-be-marketed formulation by color and embossing. The sponsor has stated that the *in vitro* dissolution profiles of the Phase 3 formulation and to-be-marketed formulation were equivalent. This was discussed in the PNDA meeting (minutes 12/14/07) and was found acceptable to the division.

The PK of saxagliptin and its major metabolite, BMS-510849 has been characterized in the PK studies. Mass balance study suggests that saxagliptin is eliminated via both

metabolic and renal pathways, while renal excretion is the primary elimination pathway for BMS-510849. BMS-510849 is formed via CYP3A4/3A5 mediated metabolism of saxagliptin. The metabolite has half the pharmacological activity of the parent drug and the systemic exposure is 2-7 times higher than those of saxagliptin. An absolute BA study has not been conducted in humans. The terminal half-life of saxagliptin and BMS-510849 was 1.2 – 3.4 h and 2.8 – 6.7 h respectively. There was no accumulation following multiple dosing.

Drug interaction was studied with metformin, glyburide, pioglitazone, digoxin, omeprazole, famotidine, drug (aluminium hydroxide+ magnesium hydroxide + simethicone) combination, simvastatin, diltiazem, and ketoconazole. Sponsor has claimed that there were no significant drug interactions observed with saxagliptin. DDI study with rifampicin is ongoing.

Initially in the development, three doses of saxagliptin (2.5, 5, and 10 mg) as film coated tablets were being studied. A definitive food effect study was conducted with the 10 mg tablets. However, based on the results of Phase 3 studies, only 2.5 mg and 5 mg tablets will be marketed. A biowaiver is being requested for conducting additional clinical food effect studies with the proposed commercial 2.5 mg and 5 mg tablets and the sponsor wants to apply the findings from the 10 mg food effect study to these lower strengths.

Saxagliptin is a chiral molecule with 4 chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. The sponsor is recommended to address the chiral conversion in humans by analyzing stored plasma samples from earlier trials using a stereo-specific assay for detection of saxagliptin and its isomer if retained samples are available. In absence of retained plasma samples from previous studies, it is recommended to conduct a study in humans to address this issue.

The listing of all Clinical Pharmacology studies is shown below:

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Single Ascending Dose Study	CV181001	Safety, PK and PD	Ascending single dose, double blind, placebo controlled	Capsule, 1 to 100 mg, oral route	72/70	Healthy	Single doses	Completed, CSR
Multiple Ascending Dose (Phase 2a Study)	CV181002	Safety, PK and PD	Ascending multiple dose, double blind, placebo controlled	Capsule, 2.5 to 50 mg, oral route	40/40	T2DM	14 days	Completed, CSR
Relative Bioavailability	CV181003	Relative bioavailability	Open-label, two-period, two-treatment cross-over study	1 x 40 mg tablet versus 2 x 20 mg oral capsules	16/16	Healthy	Single doses	Completed, CSR
¹⁴ C ADME	CV181004	Mass balance	Open-label single dose study	50 mg, oral solution	6/6	Healthy	Single dose	Completed, CSR
Ketoconazole Interaction	CV181005	Drug-drug interaction with ketoconazole	Open-label single sequence study	100 mg saxagliptin with 200 mg q12h ketoconazole, oral route	16/15	Healthy	12 days	Completed, CSR
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Multiple Ascending Dose Study	CV181010	Safety, PK and PD	Ascending multiple dose, double blind, placebo controlled	40 to 400 mg saxagliptin oral capsule	50/49	Healthy	14 days	Completed, CSR
Metformin Interaction	CV181017	Drug-drug interaction with metformin	Open-label, three period, three treatment, cross-over study balanced for residual effects	100 mg saxagliptin tablets and 1000 mg metformin tablets, oral route	18/16	Healthy	Single doses	Completed, CSR
Age/Gender	CV181018	Effect of age and gender on PK	Open-label, single dose, 2 x 2 factorial design	10 mg saxagliptin tablets, oral route	56/56	Healthy	Single dose	Completed, CSR
Renal Impairment	CV181019	PK of saxagliptin in subjects with renal impairment	Open-label, parallel group single dose study	10 mg saxagliptin tablets, oral route	40/40	Renally impaired and healthy subjects	Single dose	Completed, CSR
Hepatic Impairment	CV181020	PK of saxagliptin in subjects with hepatic impairment	Open-label, parallel group single dose study	10 mg saxagliptin tablet, oral route	36/36	Hepatically impaired and healthy subjects	Single dose	Completed, CSR

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability	CV181021	Relative bioavailability	Open-label, two-period, two-treatment cross-over study	1 x 5 mg saxagliptin tablets versus, 1 x 5 mg saxagliptin capsules, oral route	16/15	Healthy	Single doses	Completed, CSR
Effect on Lymphocyte Count	CV181022	Effects of ketoconazole and saxagliptin on lymphocyte count	Open-label, randomized, three sequence study	200 mg q12h ketoconazole and 5 and 20 mg saxagliptin tablet, oral route	36/33	Healthy	12 days	Completed, CSR
Glyburide Interaction	CV181026	Drug-drug interaction with glyburide	Open-label, randomized, three period, three treatment, cross-over study balanced for residual effects	10 mg saxagliptin tablet, 5 mg glyburide tablet, oral route	30/30	Healthy	5 days	Completed, CSR
Digoxin Interaction	CV181027	Drug-drug interaction with digoxin	Open-label, randomized, three period, three treatment,	2 x 5 mg saxagliptin tablet, digoxin 0.25 mg q6h on day 1	14/0 (terminated early)	Healthy	30 days	Terminated early due to dosing error. Abbreviated CSR with no PK.
			cross-over study	followed by digoxin 0.25 mg q12h on day 2 followed by 0.25 mg QD on days 3-7				
Pioglitazone Interaction	CV181028	Drug-drug interaction with pioglitazone	Open-label, non-randomized, sequential study	10 mg saxagliptin tablet, 45 mg pioglitazone tablet, oral route	30/28	Healthy	13 days	Completed, CSR
Effects on Lymphocyte Count and Cyanide Formation	CV181031	Effect of saxagliptin on lymphocyte count and cyanide formation	Double-blind, multiple dose, randomized, parallel group, placebo controlled	10 or 40 mg QD saxagliptin tablets, oral route	48/46	Healthy	23 days	Completed, CSR
Thorough QTc Study	CV181032	Electrocardiographic effects of saxagliptin	Randomized, double blind, four period, four treatment, cross-over study	10 or 40 mg QD saxagliptin, 400 mg QD moxifloxacin	40/35	Healthy	16 days	Completed, CSR

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Simvastatin Interaction	CV181033	Drug-drug interaction with simvastatin	Open-label, non-randomized, sequential study	10 mg saxagliptin QD, 40 mg simvastatin QD	24/23	Healthy	12 days	Completed, CSR
Definitive Food Effect	CV181034	Effect on food on the PK of saxagliptin	Open-label, randomized, two-period, two treatment, crossover study in healthy subjects	Single 10 mg saxagliptin tablets, oral route	14/14	Healthy	Single doses	Completed, CSR
Gastric Acid Controller Interaction	CV181035	Effect of Maalox Max, famotidine and omeprazole on the PK of saxagliptin	Open-label, randomized, five treatment, five period, unbalanced three way crossover study	10 mg saxagliptin tablets, 30 ml Maalox Max, 40 mg famotidine, 40 mg omeprazole, oral route	15/14	Healthy	10 days	Completed, CSR
Relative Bioavailability	CV181036	Relative bioavailability	Open label, randomized, two-period, two treatment, crossover	2 x 5 mg tablet versus 1 x 10 mg tablet	12/12	Healthy	Single doses	Completed, CSR
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability	CV181037	Relative bioavailability, PK and PD study	Open label, randomized, two-period, two treatment, crossover	5 mg saxagliptin tablet versus 5 mg saxagliptin capsules	16/15	Healthy	Single doses	Completed, CSR
Mechanism of Action	CV181041	Efficacy (effects on insulin secretion and related parameters) and safety	Double-blind, placebo-controlled study with long-term extension	5 mg saxagliptin tablets versus placebo	36/32	T2DM	Daily doses for up to 116 weeks	First 12 weeks completed, CSR (for primary endpoint/interim safety data)
Digoxin Interaction	CV181052	Drug-drug interaction with digoxin	Open label, randomized, three-period, three treatment, crossover	2 x 5 mg saxagliptin tablet, digoxin 0.25 mg q6h on day 1 followed by digoxin 0.25 mg q12h on day 2 followed by 0.25 mg QD on days 3-7	14/14	Healthy	30 days	Completed, CSR
Diltiazem Interaction	CV181053	Drug-drug interaction with diltiazem	Open-label, non-randomized.	10 mg saxagliptin tablet QD, 360 mg diltiazem QD	14/12	Healthy	11 days	Completed, CSR

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this page is the manifestation of the electronic signature.**

/s/

Jayabharathi Vaidyanathan
5/6/2009 02:14:57 PM
BIOPHARMACEUTICS

Immo Zdrojewski
5/6/2009 04:11:08 PM
BIOPHARMACEUTICS

Justin C Earp
5/6/2009 04:30:24 PM
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Christoffer Tornoe
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Wei Qiu
5/7/2009 09:57:56 AM
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Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-350	Brand Name	Not Decided
OCP Division	DCP2	Generic Name	Saxagliptin
Medical Division	DMEP	Drug Class	DPP4 Inhibitor
OCP Reviewer	Jayabharathi Valdyanathan, Ph.D.	Indication(s)	Type 2 diabetes
OCP Team Leader	Sally Choe, Ph.D.	Dosage Form	2.5 mg, 5 mg tablets
		Dosing Regimen	QD
Date of Submission	6/30/08	Route of Administration	Oral
Estimated Due Date of OCPB Review	3/13/09	Sponsor	Bristol-Myers Squibb
PDUFA Due Date	4/30/09	Priority Classification	S1
Division Due Date	4/9/09		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	22		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X			
Blood/plasma ratio:				
Plasma protein binding:	X	1		(location Pre-clinical module 4)
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3		
In-vivo effects of primary drug:	X	6		
In-vitro:	X	17		(location Pre-clinical module 4)
Subpopulation studies -				
ethnicity:				
gender:	X	1		
pediatrics:				

geriatrics: (Age)	X	1		
renal impairment:	X	1		
hepatic impairment:	X	1		
PD:				
Phase 2:		3		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				Thorough QT Study
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		67		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	YES	Reasons if the application is <u>not</u> filable (or an attachment if applicable).		
Comments sent to firm ?		<ul style="list-style-type: none"> Saxagliptin is a chiral molecule with 4 chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. The sponsor is recommended to address the chiral conversion using a stereo-specific assay for detection of saxagliptin and its isomer. 		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1) What is the exposure-response relationship for saxagliptin? 2) What is the effect of saxagliptin on QT interval? 3) Is dosing appropriate in renal and hepatic impaired patients? 4) Is dosing appropriate in elderly patients? 5) What are the possible drug interactions with saxagliptin? 		
Other comments or information not included above				
Primary reviewer Signature and Date	Jaya bharathi Vaidyanathan, Ph.D.			
Secondary reviewer Signature and Date	Sally Choe, Ph.D.			

Summary:

Saxagliptin belongs to the class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improves glycemic control in patients with type 2 diabetes by increasing the endogenous levels of the incretin hormones, GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulintropic polypeptide) by inhibiting the enzyme responsible for their degradation, DPP-4.

The Clinical Pharmacology section consist of 26 studies consisting of the following: ascending dose studies, biopharmaceutical studies, thorough QTc study, drug interaction studies, special population studies (age, gender, renal impairment and hepatic impairment), and population PK analysis. In addition there are 23 bioanalytical study reports, 17 *in vitro* metabolism/permeability studies, and one protein binding study.

The 5 mg dose is being proposed to be administered once daily regardless of food. For moderate or severe renal impairment or end stage renal disease a reduced dose of 2.5 mg is being proposed by the sponsor. No dosage adjustments are being proposed on the basis of age, gender, or race.

The Phase 3 formulation differs from the to-be-marketed formulation by color and embossing. The sponsor has stated that the *in vitro* dissolution profiles of the Phase 3 formulation and to-be-marketed formulation were equivalent. This was discussed in the PNDA meeting (minutes 12/14/07) and was found acceptable to the division.

The PK of saxagliptin and its major metabolite, BMS-510849 has been characterized in the PK studies. Mass balance study suggests that saxagliptin is eliminated via both metabolic and renal pathways, while renal excretion is the primary elimination pathway for BMS-510849. BMS-510849 is formed via CYP3A4/3A5 mediated metabolism of saxagliptin. The metabolite has half the pharmacological activity of the parent drug and the systemic exposure is 2-7 times higher than those of saxagliptin. An absolute BA study has not been conducted in humans. The terminal half-life of saxagliptin and BMS-510849 was 1.2 – 3.4 h and 2.8 – 6.7 h respectively. There was no accumulation following multiple dosing.

Drug interaction was studied with metformin, glyburide, pioglitazone, digoxin, omeprazole, famotidine, drug (aluminium hydroxide+ magnesium hydroxide + simethicone) combination, simvastatin, diltiazem, and ketoconazole. Sponsor has claimed that there were no significant drug interactions observed with saxagliptin. DDI study with rifampicin is ongoing.

Initially in the development, three doses of saxagliptin (2.5, 5, and 10 mg) as film coated tablets were being studied. A definitive food effect study was conducted with the 10 mg tablets. However, based on the results of Phase 3 studies, only 2.5 mg and 5 mg tablets will be marketed. A biowaiver is being requested for conducting additional clinical food effect studies with the proposed commercial 2.5 mg and 5 mg tablets and the sponsor wants to apply the findings from the 10 mg food effect study to these lower strengths.

Saxagliptin is a chiral molecule with 4 chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. The sponsor is recommended to address the chiral conversion in humans by analyzing stored plasma samples from earlier trials using a stereo-specific

assay for detection of saxagliptin and its isomer if retained samples are available. In absence of retained plasma samples from previous studies, it is recommended to conduct a study in humans to address this issue.

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Single Ascending Dose Study	CV181001	Safety, PK and PD	Ascending single dose, double blind, placebo controlled	Capsule, 1 to 100 mg, oral route	72/70	Healthy	Single doses	Completed, CSR
Multiple Ascending Dose (Phase 2a Study)	CV181002	Safety, PK and PD	Ascending multiple dose, double blind, placebo controlled	Capsule, 2.5 to 50 mg, oral route	40/40	T2DM	14 days	Completed, CSR
Relative Bioavailability	CV181003	Relative bioavailability	Open-label, two-period, two-treatment cross-over study	1 x 40 mg tablet versus 2 x 20 mg oral capsules	16/16	Healthy	Single doses	Completed, CSR
¹⁴ C ADME	CV181004	Mass balance	Open-label single dose study	50 mg, oral solution	6/6	Healthy	Single dose	Completed, CSR
Ketoconazole Interaction	CV181005	Drug-drug interaction with ketoconazole	Open-label single sequence study	100 mg saxagliptin with 200 mg q12h ketoconazole, oral route	16/15	Healthy	12 days	Completed, CSR
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Multiple Ascending Dose Study	CV181010	Safety, PK and PD	Ascending multiple dose, double blind, placebo controlled	40 to 400 mg saxagliptin oral capsule	50/49	Healthy	14 days	Completed, CSR
Metformin Interaction	CV181017	Drug-drug interaction with metformin	Open-label, three period, three treatment, cross-over study balanced for residual effects	100 mg saxagliptin tablets and 1000 mg metformin tablets, oral route	18/16	Healthy	Single doses	Completed, CSR
Age/Gender	CV181018	Effect of age and gender on PK	Open-label, single dose, 2 x 2 factorial design	10 mg saxagliptin tablets, oral route	56/56	Healthy	Single dose	Completed, CSR
Renal Impairment	CV181019	PK of saxagliptin in subjects with renal impairment	Open-label, parallel group single dose study	10 mg saxagliptin tablets, oral route	40/40	Renally impaired and healthy subjects	Single dose	Completed, CSR
Hepatic Impairment	CV181020	PK of saxagliptin in subjects with hepatic impairment	Open-label, parallel group single dose study	10 mg saxagliptin tablet, oral route	36/36	Hepatically impaired and healthy subjects	Single dose	Completed, CSR

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability	CV181021	Relative bioavailability	Open-label, two-period, two-treatment cross-over study	1 x 5 mg saxagliptin tablets versus, 1 x 5 mg saxagliptin capsules, oral route	16/15	Healthy	Single doses	Completed, CSR
Effect on Lymphocyte Count	CV181022	Effects of ketoconazole and saxagliptin on lymphocyte count	Open-label, randomized, three sequence study	200 mg q12h ketoconazole and 5 and 20 mg saxagliptin tablet, oral route	36/33	Healthy	12 days	Completed, CSR
Glyburide Interaction	CV181026	Drug-drug interaction with glyburide	Open-label, randomized, three period, three treatment, cross-over study balanced for residual effects	10 mg saxagliptin tablet, 5 mg glyburide tablet, oral route	30/30	Healthy	5 days	Completed, CSR
Digoxin Interaction	CV181027	Drug-drug interaction with digoxin	Open-label, randomized, three period, three treatment,	2 x 5 mg saxagliptin tablet, digoxin 0.25 mg q6h on day 1	14/0 (terminated early)	Healthy	30 days	Terminated early due to dosing error. Abbreviated CSR with no PK.
			cross-over study	followed by digoxin 0.25 mg q12h on day 2 followed by 0.25 mg QD on days 3-7				
Pioglitazone Interaction	CV181028	Drug-drug interaction with pioglitazone	Open-label, non-randomized, sequential study	10 mg saxagliptin tablet, 45 mg pioglitazone tablet, oral route	30/28	Healthy	13 days	Completed, CSR
Effects on Lymphocyte Count and Cyanide Formation	CV181031	Effect of saxagliptin on lymphocyte count and cyanide formation	Double-blind, multiple dose, randomized, parallel group, placebo controlled	10 or 40 mg QD saxagliptin tablets, oral route	48/46	Healthy	23 days	Completed, CSR
Thorough QTc Study	CV181032	Electrocardiographic effects of saxagliptin	Randomized, double blind, four period, four treatment, cross-over study	10 or 40 mg QD saxagliptin, 400 mg QD moxifloxacin	40/35	Healthy	16 days	Completed, CSR

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Simvastatin Interaction	CV181033	Drug-drug interaction with simvastatin	Open-label, non-randomized, sequential study	10 mg saxagliptin QD, 40 mg simvastatin QD	24/23	Healthy	12 days	Completed, CSR
Definitive Food Effect	CV181034	Effect on food on the PK of saxagliptin	Open-label, randomized, two-period, two treatment, crossover study in healthy subjects	Single 10 mg saxagliptin tablets, oral route	14/14	Healthy	Single doses	Completed, CSR
Gastric Acid Controller Interaction	CV181035	Effect of Maalox Max, famotidine and omeprazole on the PK of saxagliptin	Open-label, randomized, five treatment, five period, unbalanced three way crossover study	10 mg saxagliptin tablets, 30 ml Maalox Max, 40 mg famotidine, 40 mg omeprazole, oral route	15/14	Healthy	10 days	Completed, CSR
Relative Bioavailability	CV181036	Relative bioavailability	Open label, randomized, two-period, two treatment, crossover	2 x 5 mg tablet versus 1 x 10 mg tablet	12/12	Healthy	Single doses	Completed, CSR
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen (mg); Route of Administration	Number of Subjects (dosed /completed)	Target Population	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability	CV181037	Relative bioavailability, PK and PD study	Open label, randomized, two-period, two treatment, crossover	5 mg saxagliptin tablet versus 5 mg saxagliptin capsules	16/15	Healthy	Single doses	Completed, CSR
Mechanism of Action	CV181041	Efficacy (effects on insulin secretion and related parameters) and safety	Double-blind, placebo-controlled study with long-term extension	5 mg saxagliptin tablets versus placebo	36/32	T2DM	Daily doses for up to 116 weeks	First 12 weeks completed, CSR (for primary endpoint/interim safety data)
Digoxin Interaction	CV181052	Drug-drug interaction with digoxin	Open label, randomized, three-period, three treatment, crossover	2 x 5 mg saxagliptin tablet, digoxin 0.25 mg q6h on day 1 followed by digoxin 0.25 mg q12h on day 2 followed by 0.25 mg QD on days 3-7	14/14	Healthy	30 days	Completed, CSR
Diltiazem Interaction	CV181053	Drug-drug interaction with diltiazem	Open-label, non-randomized,	10 mg saxagliptin tablet QD, 360 mg diltiazem QD	14/12	Healthy	11 days	Completed, CSR

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Jayabharathi Vaidyanathan
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Sally Choe
9/8/2008 12:27:20 PM
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