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 ±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 ±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

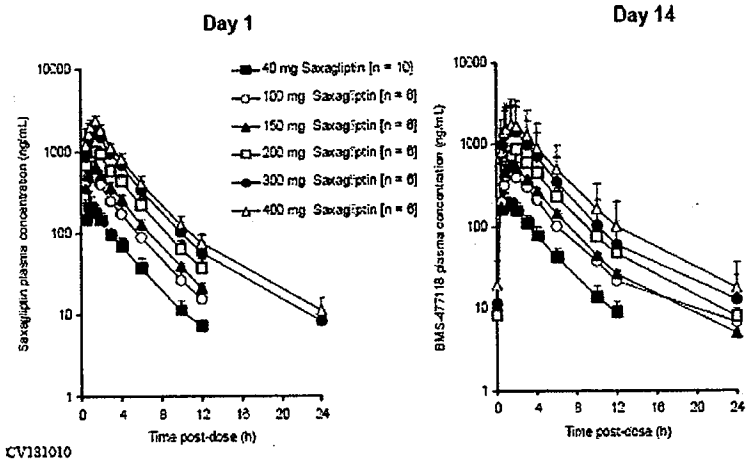


Table 1: Summary Statistics for Saxagliptin PK Parameters

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]
Cmax (ng/mL) Geometric Mean (C.V. %)	40 mg	226 (49)	224 (53)
	100 mg	585 (19)	487 (14)
	150 mg	694 (25)	614 (19)
	200 mg	1207 (11)	985 (22)
	300 mg	1845 (20)	1630 (31)
	400 mg	2321 (18)	1861 (22)
AUC(TAU) (ng·h/mL) Geometric Mean (C.V. %)	40 mg	739 (26)	800 (24)
	100 mg	1899 (18)	1991 (11)
	150 mg	2543 (11)	2532 (9)
	200 mg	4186 (15)	4090 (10)
	300 mg	6652 (22)	6539 (20)
	400 mg	8364 (14)	8532 (13)
A.I. for AUC(TAU) Geometric Mean (C.V. %)	40 mg	N/A	1.08 (13)
	100 mg		1.05 (15)
	150 mg		1.00 (13)
	200 mg		0.99 (19)
	300 mg		0.98 (14)
	400 mg		1.02 (8)
Tmax (h) Median (Min, Max)	40 mg	1.00 (0.75, 2.00)	0.88 (0.50, 2.00)
	100 mg	1.13 (0.50, 2.00)	1.50 (0.50, 2.00)
	150 mg	1.50 (0.50, 2.00)	1.25 (0.75, 2.00)
	200 mg	1.50 (0.50, 2.00)	1.50 (0.75, 2.00)
	300 mg	1.50 (1.00, 1.50)	1.75 (1.00, 2.00)
	400 mg	1.50 (1.00, 1.50)	1.50 (0.75, 2.00)
T-HALF (h) Mean (S.D.)	40 mg	2.29 (0.18)	3.46 (0.29)
	100 mg	2.32 (0.22)	3.03 (1.29)
	150 mg	2.27 (0.14)	2.69 (0.91)
	200 mg	2.25 (0.21)	3.58 (1.25)
	300 mg	2.88 (0.85)	5.38 (3.44)
	400 mg	3.79 (1.11)	5.48 (2.55)

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]
%UR 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	259 (77)	220 (78)
	100 mg	183 (56)	221 (90)
	150 mg	169 (54)	230 (82)
	200 mg	199 (69)	241 (36)
	300 mg	191 (68)	196 (37)
	400 mg	213 (80)	159 (91)

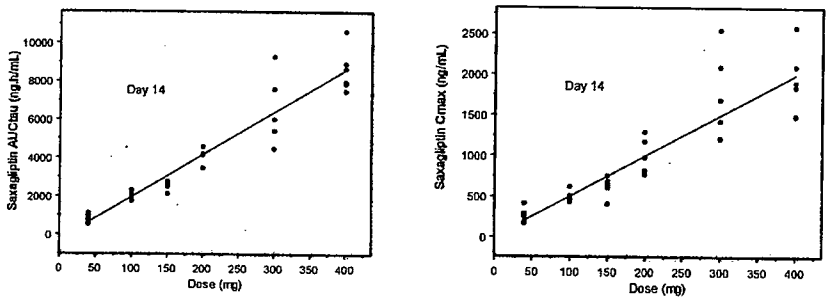
Dose Proportionality: *Dose proportionality was estimated using the power model, ($Y = \alpha \cdot Dose^{\beta}$ where Y, α and β correspond to the PK parameter (AUC or Cmax),*

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[Cmax] on log(dose) and of log[AUC] on log(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:

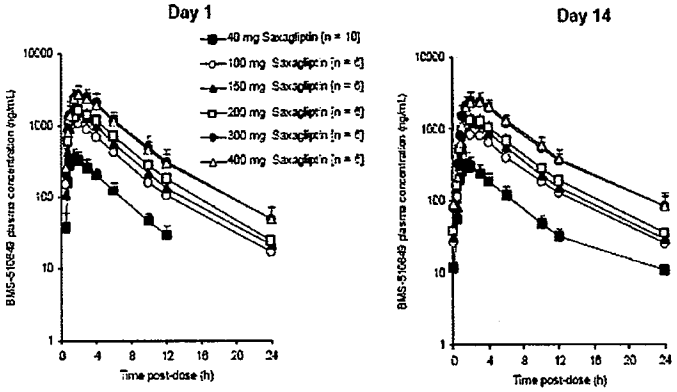
Cmax Day 1: 1.00 [0.84 – 1.17]
Cmax Day 14: 0.95 [0.755 – 1.14]
AUC Day 1: 1.06 [0.93 – 1.20]
AUC Day 14: 1.03 [0.87 – 1.18]

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 Cmax 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) [4]
Cmax (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)	1589 (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)	1708 (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	N/A	0.98 (15)
	100 mg		0.94 (11)
	150 mg		0.94 (5)
	200 mg		0.92 (6)
	300 mg		1.04 (11)
	400 mg		1.10 (10)
Molar Ratio for AUC(TAU) [3] 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 (25)	1.85 (21)
Tmax (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)

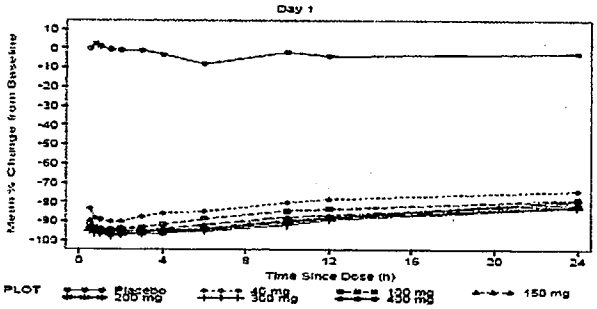
BMS-510849 PK Parameter	Saxagliptin Dose	Study Day	
		Day 1 (n=10 for 40 mg) (n=6 for all other doses)	Day 14 (n=10 for 40 mg) (n=6 for all other doses) [a]
T-HALF (h) Mean (S.D.)	40 mg	2.96 (0.29)	5.71 (1.05)
	100 mg	4.44 (0.31)	5.86 (1.85)
	150 mg	4.19 (0.54)	5.84 (1.96)
	200 mg	4.08 (0.14)	5.98 (1.85)
	300 mg	4.27 (0.32)	7.24 (2.03)
	400 mg	4.41 (0.55)	7.38 (1.71)
%UR Mean (S.D.)	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)
	400 mg	26 (7)	21 (10)
CLR (mL/min) Mean (S.D.)	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 (33)	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 Tmax 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):



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.