2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Pharmacokinetics: Absorption After a Single Dose (Saxagliptin, Rat)

Study Description or Title: **Pharmacokinetics of Saxagliptin and BMS-510849 in Sprague-Dawley Rats following Single Dose Intravenous or Oral Administration of Saxagliptin**

			Test Article:	**Saxagliptin**
			Study Type:	**Non-GLP**
			Location in Dossier:	
			Study No./Document Control Number:	MAP005-477118/930000866
Species/Strain:	Rat/Sprague-Dawley			
Gender (M/F) / Number of Animals:	Male / 2 per treatment		Male / 2 per treatment	
Feeding condition:	Fasted overnight and fed 4 h after dosing		Fasted overnight and fed 4 h after dosing	
Vehicle/Formulation:	Water		Water	
Method of Administration:	IV Bolus		Oral gavage	
Sample (Whole blood, plasma, serum etc.):	Plasma		Plasma	
Analytes:	Saxagliptin and BMS-510849		Saxagliptin and BMS-510849	
Assay:	LC/MS/MS		LC/MS/MS	
Saxagliptin Dose (mg/kg):	10		8	
Route:	**IV**		**PO**	
Parameter	**Saxagliptin**	**BMS-510849[a]**	**Saxagliptin**	**BMS-510849[a]**
Cmax (µg/mL)	5.2	0.2	0.5	0.2
AUC(0-infinity) (µgxh/mL)	1.6	0.3	0.9	0.4
Tmax (h)	-	0.3	0.7	1.1
CLTp (mL/min/kg)	115	ND	-	-
Vss (L/kg)	5.2	ND	-	-
T1/2 (h)	2.1	ND	-	-
% dose excreted unchanged in urine (0-10 h)	33	-	ND	-
Bioavailability (%)	-	-	75	-

Additional Information: ND = not determined.
Saxagliptin was well, rapidly absorbed, and rapidly cleared in rats. Saxagliptin was excreted in urine as parent. The Vss value indicated extravascular distribution of saxagliptin.

[a] The bioanalytical assay that was used to measure concentrations of BMS-510849 in this study may not have been completely specific for BMS-510849. Other mono-hydroxylated metabolites with the same MRM transition as BMS-510849 in the LC/MS/MS (332 → 196) may have co-eluted with BMS-510849 under the conditions employed in the assay. Therefore the reported concentration values for BMS-510849 may include BMS-510849 and other mono-hydroxylated metabolites. The measurement of saxagliptin was not impacted in this method.

Pharmacokinetics: Absorption After a Single Dose (BMS-510849, Rat)

Study Description or Title: Pharmacokinetics of BMS-510849 in Sprague-Dawley Rats following Single Dose Intravenous, Subcutaneous, and Oral Administration of BMS-510849

Test Article: BMS- 510849
Study Type: Non-GLP
Location in Dossier:
Study No./Document Control Number: TSU3725/930023244

Species/Strain:	Rat/Harlan Sprague-Dawley				
Gender (M/F) / Number of Animals:	Male / 3 per dose	Male / 3 per dose		Male/ 3 per dose[a]	
Feeding condition:	Fasted overnight and fed 4 h after dosing	Fasted overnight and fed 4 h after dosing		Fasted overnight and fed 4 h after dosing	
Vehicle/Formulation:	10 mM citrate buffer, pH 4/solution	10 mM citrate buffer, pH 4/solution		0.5% Methocel A4M (citrate buffered, pH 4)/suspension	
Method of Administration:	IV Bolus	Subcutaneous		Oral gavage	
Sample (Whole blood, plasma, serum etc.):	Plasma	Plasma		Plasma	
Analyte:	BMS-510849	BMS- 510849		BMS- 510849	
Assay:	LC/MS/MS	LC/MS/MS		LC/MS/MS	
BMS-510849 Dose (mg/kg):	75	150	300	600	1200
Route:	IV	SC		PO	
Parameter					
Cmax (µg/mL)	298 ± 26.1	84.5 ± 14.8	136 ± 19.2	2.00, 6.30	6.14, 5.91
AUC(0-infinity) (µg*h/mL)	52.9 ± 7.38	137 ± 42.3	274 ± 15.6	9.74, 17.9	29.5, 28.1
Tmax (h)	0.0333 ± 0.00	0.583 ± 0.144	0.583 ± 0.144	1.00, 1.00	0.500, 1.00
CLTp (L/h/kg)	1.43 ± 0.186	-	-	-	-
Vss (L/kg)	0.920 ± 0.203	-	-	-	-
T1/2 (h)	11.4 ± 2.21	-	-	-	-
Bioavailability (%)	-	129	129	2.30, 4.23	3.49, 3.32

Additional Information: BMS-510849 was poorly absorbed in rats following oral administration. However, the absorption was approximately complete following subcutaneous administration.

[a] Individual animal values of pharmacokinetic parameters are listed instead of group mean ± SD values; pharmacokinetic parameters were only determined in 2 of 3 rats in the oral dosing groups because incomplete concentration versus time profiles were obtained from 1 rat/group.

Pharmacokinetics: Absorption After a Single Dose (Saxagliptin, Dog)

Study Description or Title: Pharmacokinetics of Saxagliptin in Beagle Dogs following a Single Dose Intravenous or Oral Administration of Saxagliptin

Test Article: Saxagliptin
Study Type: Non-GLP
Location in Dossier:
Study No./Document Control Number: MAP005-477118/930000866

Species/Strain:	Dog/Beagle		
Gender (M/F) / Number of Animals:	Male / 2 per treatment	Male / 2 per treatment	
Feeding condition:	Fasted overnight and fed 4 h after dosing	Fasted overnight and fed 4 h after dosing	
Vehicle/Formulation:	Water	Water	
Method of Administration:	IV infusion (10 min)	Oral gavage	
Sample (Whole blood, plasma, serum etc.):	Plasma	Plasma	
Analyte:	Saxagliptin	Saxagliptin	
Assay:	LC/MS/MS	LC/MS/MS	
Saxagliptin Dose (mg/kg):	5.9	5.2	
Route:	IV	PO	
Parameter			
Cmax (µg/mL)	10.1	2.7	
AUC(0-infinity) (µgxh/mL)	10.7	7.3	
Tmax (h)	-	1.2	
CLTp (mL/min/kg)	9.3	-	
Vss (L/kg)	1.3	-	
T1/2 (h)	3.0	-	
Amount excreted unchanged in urine (0-24 h, %)	40	ND	
Bioavailability (%)	-	76	

Additional Information: ND = not determined
Saxagliptin was well and rapidly absorbed in dogs. Saxagliptin showed intermediate clearance, and was excreted in urine as parent.

Pharmacokinetics: Absorption After a Single Dose (Saxagliptin, Monkey)

Study Description or Title: **Pharmacokinetics of Saxagliptin in Cynomolgus Monkeys following Single Dose Intravenous or Oral Administration of Saxagliptin**

Test Article: **Saxagliptin**
Study Type: **Non-GLP**
Location in Dossier:
Study No./Document Control Number: MAP005-477118/930000866

Species/Strain:	Monkey/Cynomolgus	
Gender (M/F) / Number of Animals:	Male / 2 per treatment[a]	Male / 2 per treatment
Feeding condition:	Fasted overnight and fed 4 h after dosing	Fasted overnight and fed 4 h after dosing
Vehicle/Formulation:	Water	Water
Method of Administration:	IV infusion (10 min)	Oral gavage
Sample (Whole blood, plasma, serum etc.):	Plasma	Plasma
Analyte:	Saxagliptin	Saxagliptin
Assay:	LC/MS/MS	LC/MS/MS
BMS-477118 Dose (mg/kg):	3.4	3.4
Route:	**IV**	**PO**
Parameter		
Cmax (µg/mL)	5.4	1.0
AUC(0-infinity) (µgxh/mL)	3.9	2.0
Tmax (h)	-	1.0
CLTp (mL/min/kg)	14.5	-
Vss (L/kg)	1.8	-
T1/2 (h)	4.4	-
% dose excreted unchanged in urine (0-24 h)	60	ND
Bioavailability (%)	-	51

Additional information: ND = not determined. Saxagliptin was rapidly absorbed in monkeys. The oral bioavailability was approximately 51%. Saxagliptin showed moderate to high clearance and was extensively eliminated in urine.

[a] Pharmacokinetic parameters were determined in only 1 of 2 monkeys assigned to intravenous administration; the second monkey administered saxagliptin intravenously was euthanized 4 hours after drug administration.

Pharmacokinetics: Organ Distribution (Tissue: Plasma Concentration Ratios)

Study Description or Title: **Tissue Distribution of Radioactivity in Male Long-Evans Rats following Oral Administration of [^{14}C]Saxagliptin**

Test Article: **[^{14}C]Saxagliptin**
Study Type: **Non-GLP**
Location in Dossier:
Study No./Document Control No.: **DDBS038/930007588**

Species:	Long-Evans Rats
Gender (M/F) / Number of Animals:	Male / 24 (3 rats per time point)
Feeding condition:	Fasted overnight and for 4 h after dosing, then fed *ad libitum* for the remainder of the study
Vehicle/Formulation:	0.011 M hydrochloric acid in water
Method of Administration:	Oral
Dose (mg/kg):	20 mg/kg (100 µCi/kg)
Radionuclide:	^{14}C
Specific Activity:	5.84 µCi/mg
Sampling time:	0, 1, 4, 12, 24, 48, 96 and 168 h

Matrix	**Tissue:Plasma Concentration Ratios**		
	1 h	**4 h**	**12 h**
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Adipose (epididymal)	0.11 ± 0.03	0.08 ± 0.07	0.32 ± 0.55
Adipose (visceral)	0.51 ± 0.18	0.30 ± 0.36	0.95 ± 0.62
Adipose (subcutaneous)	0.30 ± 0.08	0.31 ± 0.05	0.00 ± 0.00

Pharmacokinetics: Organ Distribution (Tissue: Plasma Concentration Ratios)

Study Description or Title: **Tissue Distribution of Radioactivity in Male Long-Evans Rats following Oral Administration of [^{14}C]Saxagliptin**

Test Article: **[^{14}C]Saxagliptin**

Study Type: **Non-GLP**

Location in Dossier:

Study No./Document Control No.: **DDBS038/930007588**

Matrix	Tissue:Plasma Concentration Ratios		
	1 h	4 h	12 h
	Mean ± SD	Mean ± SD	Mean ± SD
Adrenal Glands	0.99 ± 0.12	0.91 ± 0.10	2.18 ± 0.27
Blood	0.71 ± 0.05	0.88 ± 0.04	1.55 ± 0.31
Bone (femur)	0.16 ± 0.03	0.13 ± 0.12	0.00 ± 0.00
Bone Marrow (femur)	0.83 ± 0.08	0.85 ± 0.04	2.19 ± 0.12
Brain	0.04 ± 0.01	0.68 ± 1.07	0.34 ± 0.18
Cecum	0.43 ± 0.05	36.51 ± 33.23	95.79 ± 67.45
Duodenum	5.38 ± 1.40	8.72 ± 1.39	3.81 ± 0.21
Eyes	0.34 ± 0.01	0.91 ±0.24	4.17 ± 1.06
Heart	0.51 ± 0.02	0.55 ± 0.05	1.27 ± 0.26
Ileum	1.68 ± 0.81	245.17 ± 205.25	8.77 ± 1.46
Intestine, Large	0.82 ± 0.17	4.01 ± 2.07	61.23 ± 27.13
Jejunum	37.12 ± 7.41	25.21 ± 29.07	8.05 ± 1.96
Kidneys	4.50 ± 0.31	5.32 ± 0.54	20.22 ± 4.86
Liver	17.18 ± 2.23	32.91 ± 10.34	74.05 ± 9.79
Lungs	0.91 ± 0.07	1.31 ± 0.08	3.65 ± 0.44
Pancreas	0.95 ± 0.03	1.02 ± 0.14	1.42 ± 0.17
Skeletal Muscle (pectoral)	0.40 ± 0.04	0.38 ± 0.10	0.18 ± 0.31
Skeletal Musole (thigh)	0.40 ± 0.04	0.38 ± 0.04	1.20 ± 0.15
Skin, Nonpigmented	0.55 ± 0.02	0.73 ± 0.08	0.48 ± 0.84
Skin, Pigmented	0.58 ± 0.08	1.11 ± 0.41	5.63 ± 5.45
Spleen	0.84 ± 0.07	0.73 ± 0.14	2.63 ± 0.38
Stomach	2.30 ± 1.36	1.14 ± 0.15	1.12 ± 0.18
Testes	0.25 ± 0.02	0.66 ± 0.07	1.54 ± 0.41
Thyroid	1.53 ± 0.20	1.24 ± 0.30	1.23 ± 2.13
Urinary Bladder	5.33 ± 3.29	41.97 ± 53.88	22.78 ± 17.26

Additional Information: Tissue:plasma ratios are only reported through the 12 h time point since plasma levels of radioactivity were not measurable after 12 h.

Pharmacokinetics: Organ Distribution (Mean Percentage of Radioactive Dose in Rat Tissues)

Study Description or Title: Tissue Distribution of Radioactivity in Male Long-Evans Rats following Oral Administration of [^{14}C]Saxagliptin

Test Article: [^{14}C]Saxagliptin
Study Type: Non-GLP
Location in Dossier:
Study No./Document Control No.: DDBS038/930007588

Species/Strain: Rat/Long-Evans
Gender (M/F) / Number of Animals: M/24 (3 rats per time point)
Feeding condition: Fasted overnight and for 4 h after dosing, then fed *ad libitum* for the remainder of the study
Vehicle/Formulation: 0.011 M hydrochloric acid in water
Method of Administration: Oral
Dose (mg/kg): 20 mg /kg (100 µCi/kg)
Radionuclide: ^{14}C
Specific Activity: 5.84 µCi/mg
Sampling time: 0, 1, 4, 12, 24, 48, 96 and 168 h

Tissues/Organs	Mean Percentage of the Radioactive Dose in Tissues and Gastrointestinal Tract Tissues						
	1 h	4 h	12 h	24 h	48 h	96 h	168 h
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Adipose (subcutaneous)	0.63 ± 0.22	0.14 ± 0.02	ND	ND	ND	ND	ND
Adrenal Glands	ND	ND	ND	ND	ND	ND	ND
Blood	1.04 ± 0.06	0.30 ± 0.04	0.06 ± 0.00	ND	ND	ND	ND
Bone (femur)	0.16 ± 0.03	0.03 ± 0.03	ND	ND	ND	ND	ND
Bone Marrow (femur)	0.05 ± 0.01	0.01 ± 0.00	ND	ND	ND	ND	ND
Brain	0.00 ± 0.01	0.02 ± 0.03	ND	ND	ND	ND	ND
Cecum	0.04 ± 0.01	0.65 ± 0.50	0.29 ± 0.25	0.00 ± 0.01	ND	ND	ND
Cecum Contents	0.22 ± 0.22	21.07 ± 0.33	7.74 ± 6.23	0.18 ± 0.08	0.06 ± 0.03	ND	ND
Duodenum	0.23 ± 0.01	0.30 ± 0.08	0.01 ± 0.01	0.00 ± 0.01	ND	ND	ND
Eyes	0.01 ± 0.00	ND	ND	ND	ND	ND	ND
Heart	0.05 ± 0.01	0.01 ± 0.00	ND	ND	ND	ND	ND
Ileum	0.06 ± 0.03	8.48 ± 5.38	0.02 ± 0.01	0.01 ± 0.00	ND	ND	ND
Intestinal Contents, Large	0.09 ± 0.06	0.14 ± 0.13	8.16 ± 7.39	0.21 ± 0.15	0.03 ± 0.03	ND	ND
Intestinal Contents, Small	29.71 ± 9.66	9.69 ± 5.61	0.34 ± 0.11	0.07 ± 0.03	0.02 ± 0.02	ND	ND
Intestine, Large	0.13 ± 0.04	0.12 ± 0.07	0.24 ± 0.12	0.01 ± 0.00	ND	ND	ND
Jejunum	10.38 ± 2.05	0.61 ± 0.67	0.06 ± 0.01	0.01 ± 0.01	0.00 ± 0.01	ND	ND
Kidneys	0.67 ± 0.10	0.20 ± 0.02	0.08 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.01 ± 0.00	ND
Liver	10.71 ± 0.99	4.97 ± 0.99	1.60 ± 0.20	0.54 ± 0.25	0.14 ± 0.03	0.07 ± 0.01	0.03 ± 0.01
Lungs	0.08 ± 0.01	0.03 ± 0.01	0.01 ± 0.00	ND	ND	ND	ND
Pancreas	0.07 ± 0.02	0.01 ± 0.00	ND	ND	ND	ND	ND
Skeletal Muscle (thigh)	3.70 ± 0.27	0.81 ± 0.16	0.30 ± 0.03	0.04 ± 0.06	ND	ND	ND
Skin, Nonpigmented	1.08 ± 0.09	0.33 ± 0.07	0.03 ± 0.05	ND	ND	ND	ND
Skin, Pigmented	0.57 ± 0.01	0.25 ± 0.11	0.13 ± 0.10	0.01 ± 0.01	0.02 ± 0.03	0.01 ± 0.01	ND
Spleen	0.04 ± 0.00	0.01 ± 0.00	ND	ND	ND	ND	ND
Stomach	0.31 ± 0.16	0.04 ± 0.01	ND	ND	ND	ND	ND
Stomach Contents	2.90 ± 3.40	0.03 ± 0.02	ND	ND	ND	ND	ND
Testes	0.05 ± 0.01	0.03 ± 0.00	0.01 ± 0.00	ND	ND	ND	ND
Thyroid	ND	ND	ND	ND	ND	ND	ND
Urinary Bladder	0.03 ± 0.02	0.07 ± 0.09	0.01 ± 0.01	ND	ND	ND	ND

Abbreviations: SD = Standard Deviation; ND = Not detected. Concentrations of [^{14}C]saxagliptin-derived radioactivity were below the limit of quantification.

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